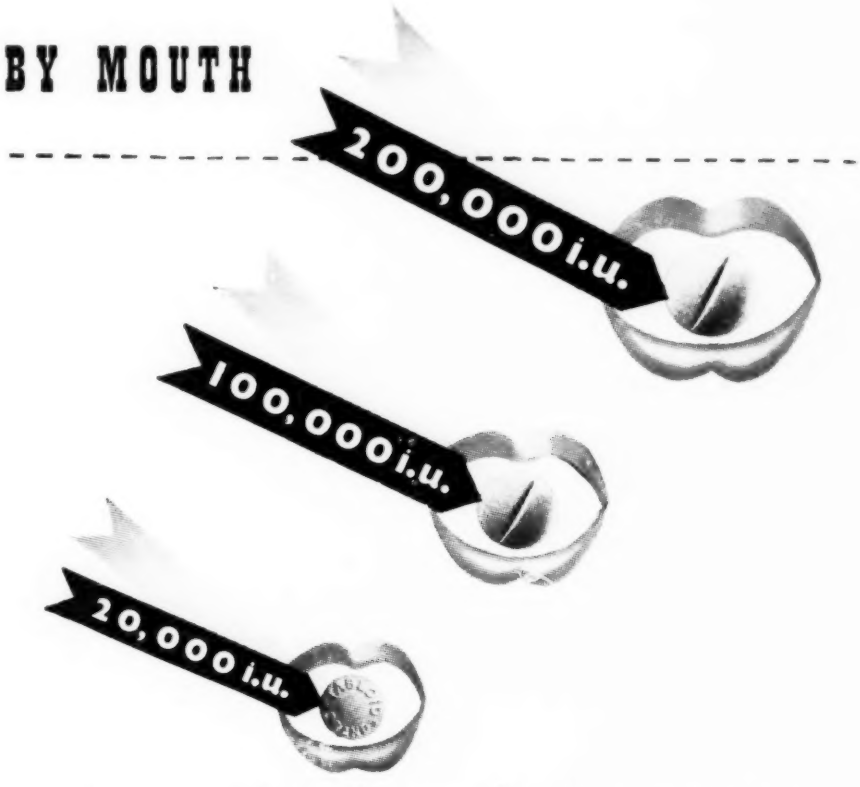
BY MOUTH



the simplest form of administration

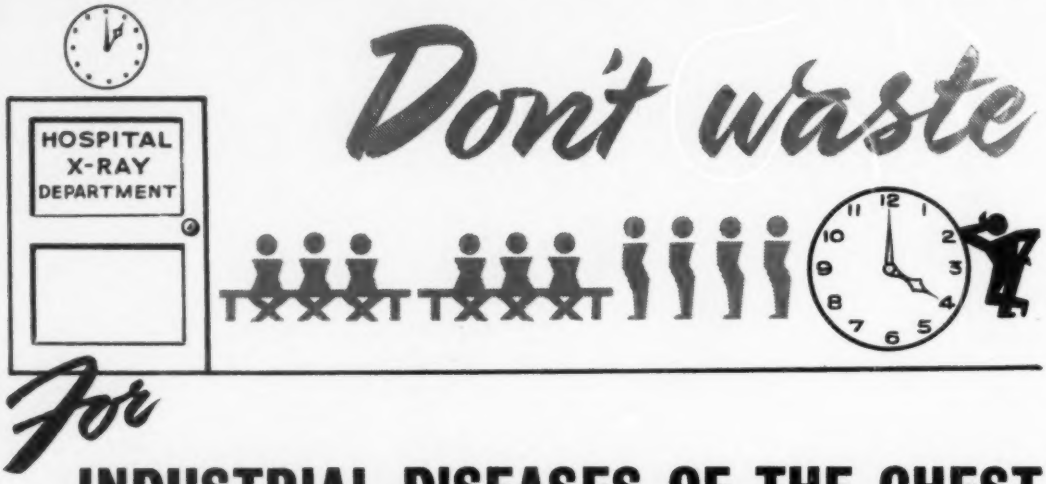
Penicillin by mouth has manifold advantages. 'Tabloid' Penicillin Oral:

- Obviates the discomfort of injections.
- Is preferred by the patient.
- Reduces demands on the practitioner's time.
- Is especially useful for children.

'Tabloid' Penicillin Oral may be used alone or as an adjunct to parenteral penicillin—for example, to maintain adequate blood levels at night. For conditions requiring high dosage, a new strength—200,000 i.u.—is now available in addition to the 20,000 i.u. and 100,000 i.u. already issued.

'TABLOID' PENICILLIN ORAL

BURROUGHS WELLCOME & CO. (The Wellcome Foundation Ltd.) LONDON



Don't waste

For

INDUSTRIAL DISEASES OF THE CHEST

The Mobile Units of Portable X-Rays Ltd. X-ray employees on site at the factory, thus avoiding constant visits to hospital with the inevitable absence from productive work. The saving effected by this means will be found to be very considerable both in time and money.

The Mobile X-ray units of Portable X-Rays Ltd. are now being regularly employed by large industrial organisations. Demonstrations are offered free and without obligation.

Full details will gladly be sent on request.

PORTABLE X-RAYS LTD
POWER ROAD
CHISWICK
LONDON, W.4
CHIswick 7836-7

FREE DEMONSTRATION ON REQUEST

man-hours —

save them by using...

MOBILE X-RAY EXAMINATION ON SITE

(Time occupied 5 minutes per man)

Full details will gladly be sent on request.

PORTABLE X-RAYS

NIGHT Ltd & DAY

When the problem is **haemorrhage** *or* **shock**

'PLASMOSAN'
trade mark *brand*
polyvinylpyrrolidone solution

fulfils the requirements of a plasma substitute in that

1 Its viscosity, colloidal osmotic pressure and tonicity approximate closely to those of blood.

2 It has a high margin of safety, is non-antigenic and non-pyrogenic.

3 It is retained in the body for a sufficient time to allow the restoration of the plasma proteins.

4 It is not stored in the tissues.

5 It does not affect kidney function nor disturb blood grouping or clotting.

'PLASMOSAN' provides a sound and effective means of restoring the blood pressure in cases of injury, and of maintaining it during operation. Its particular value is that it is ready for immediate use in any amount, and can be administered without the time-consuming investigations which are necessary before blood transfusion.

We shall be pleased to send detailed literature on request.

'PLASMOSAN' *is supplied in standard transfusion bottles of 540 c.c. in cartons of 4.*

manufactured by
MAY & BAKER LTD

MA277

distributors
PHARMACEUTICAL SPECIALITIES (MAY & BAKER) LTD DAGENHAM

ELASTOCREPE

valuable in the after-treatment of
VARICOSE VEINS and ULCERS

ELASTOCREPE complies with the Drug Tariff specification for "Cotton crepe bandage" and may be prescribed by name.

★ Three widths are available for the N.H.S.—2½", 3" and 4" by 5 yards stretched.

★ ***PRESCRIBE IT BY NAME ON ALL SCRIPTS WHEN COTTON CREPE BANDAGE IS REQUIRED***

ELASTOCREPE *is made in England by* T. J. SMITH & NEPHEW LTD., HULL.
Outside the British Commonwealth Elastocrepe is known as Tensocrepe.

Brit. J. industr. Med., 1952, **9**, 1.

RHEUMATISM IN MINERS

PART 1: RHEUMATIC COMPLAINTS

BY

J. S. LAWRENCE and JEAN AITKEN-SWAN

From the Walkden Miners' Clinic and the Departments of Rheumatism Research and Occupational Health, Manchester University

(RECEIVED FOR PUBLICATION AUGUST 18, 1951)

Much has been written about the heavy toll of rheumatism in industry (Kahlmeter, 1923; Newman, 1924; Horder, 1944), but there is little precise information as to its incidence in the general population. Such information as exists indicates that some 3% of the insured population are incapacitated each year because of the rheumatic diseases (Report on Incapacitating Sickness in the Insured Population of Scotland, 1930–36). The proportion of the population consulting general practitioners is rather similar, varying from 2·8% in the south of England to 4·3% in the north of Scotland (Newman, 1924; Davidson and Duthie, 1937). The consultation and incapacity rates, however, are but a poor guide to incidence, and this applies perhaps to the rheumatic diseases more than to any others. Popular belief in the incurability of these disorders is strongly held and induces an attitude of resignation which the medical profession has so far done little to dispel.

The nearest attempt to a determination of total rheumatic incidence is that reported by Stocks (1949) based on a sickness survey for the Central Office of Information. From this survey a monthly incidence of 18% of rheumatic diseases in the population is deduced. This, however, is based on self-diagnosis.

On the incidence of rheumatism in miners information is even less definite, but there have been indications that it is higher than in the general population. Thus in Scotland in 1938, 5% of miners were incapacitated from this cause. This figure may be compared with an incapacity rate of 3% in metal and transport workers and in general labourers, and 2% in the remaining occupation groups studied. The incapacity rate was thus roughly twice as great in miners, and the increase was distributed equally amongst joint, muscular, and neuritic forms (Scottish Report on Chronic Rheumatic Diseases, 1945).

Method of Study

The present investigation was undertaken at the request of the Miners' Welfare Commission and was carried out in the Manchester coal fields. A preliminary survey in a number of pits in the area revealed the practical difficulties which would result from the application of random sampling methods to an underground population, and it was decided to survey the entire population of one mine. For this purpose the Bedford Colliery at Leigh was chosen. In addition a survey was made of the following groups: (1) the workers at an engineering yard belonging to the National Coal Board: (2) office staff employed at the Area Headquarters of the National Coal Board; (3) the Bedford miners' families; and (4) a random sample of the town of Leigh.

Bedford Colliery.—Bedford is a medium-sized colliery employing just over 1,000 men. Of these some 80% work underground, 43% at the coal face, and the remainder on the roadways or at miscellaneous sites. At the time of the survey three seams were being worked. Two of these were machine-operated and had a roof-height of 3 ft. 3 in. The third was higher, 6 to 8 ft., and worked by hand. It has since been closed. Temperatures underground were moderate, varying from 75 to 86 F. at the coal face, and the workings were dry. Part of the journey to the coal face was by man-train so that not more than one and a half miles had to be walked to the furthest face. This is an average distance under present conditions, and in fact this colliery may be taken as fairly representative of mining practice in the district.

Engineering Yard.—The Walkden yard is owned by the National Coal Board and is designed to carry out light constructional and repair work. It employs blacksmiths, machinists, carpenters,

painters, and others. In all, there are 575 male employees in addition to 14 female office staff. Of the males, 76 had at some time worked underground so that there were 499 non-mining males in this survey.

Walkden Offices.—These constitute the headquarters of the area and have a staff of 370, mostly clerks and typists. There are 232 males and 138 females. Of the males 28 had at some time worked underground so that there were 204 non-mining males in this study. As the Bedford miners and the workers at the Walkden yard and offices were all interviewed by the same person (J. S. L.), they form directly comparable groups of miners and non-miners, and problems of observer error are thus minimized.

Bedford Families.—As most of the Bedford miners live in the town of Leigh the work of visiting their homes was greatly facilitated. All relatives over the age of 15 were seen during the course of the families' survey and also relatives by marriage provided that they were normally resident in the miner's home. Of the persons interviewed in the families' survey approximately 40% were wives of the miners, 20% sons and daughters, 13% fathers and mothers, and 8% brothers and sisters. The remaining 20% were in-laws and other relations.

Leigh Survey.—Leigh is an industrial town of some 48,000 inhabitants, situated 12 miles west of Manchester. The town is low-lying on clay soil, its highest point being only 135 feet above sea level. The two main industries are cotton weaving and spinning, and coal mining, and these occupations absorb the majority of workers and school-leavers. Among the other industries to be found in the town are engineering, a brush works, a clothing factory, iron foundries, an agricultural implement factory, and a cable works.

Many of the houses are over 60 years old and lack baths or hot water. These houses are usually of the "two up—two down" type and many are damp; indeed it is probable that some 75% of houses in Leigh have some degree of dampness.

In the Leigh survey a random sample of households was selected from the electoral roll of the Borough, supplemented by a list supplied by the housing department of the newly erected and occupied houses not yet included in the electoral roll. Every tenth address was taken, making a total of 1,393 houses, and all individuals normally resident in the house and over the age of 15 were asked to cooperate in the survey. The random sample contained a number of Bedford Colliery families, 63 in all, and these, having already been included in the families' survey, were not counted again in the Leigh survey, the figures for each survey being therefore unduplicated.

Composition of Groups Studied.—For the purposes of this study the males have been divided into miners and non-miners, and the females into those from mining and non-mining families. Miners were defined as those who had at some time in their lives worked wholetime underground for at least a month. Mining families in the Leigh survey were those in which at least one member of the family had worked for not less than five years underground. For the Bedford Colliery this criterion was not used and the families of all workers were included with the mining families. The following are the final groupings.

Males

Miners :	
Bedford Colliery	987
Families' survey (working at collieries other than Bedford)	220
Leigh survey (working at collieries other than Bedford)	535
Total miners	1,742
Non-miners :	
Leigh survey	929
Walkden Yard	499
Walkden Offices	204
Families' survey	299
Total non-miners	1,931

Females

Mining Families :	
Families' survey	1,296
Leigh survey	639
Total females from mining families	1,935
Non-mining families, Leigh survey	822
Family status unknown, Leigh survey	328

Interviews.—Employees at the Bedford Colliery, the Walkden yard and offices were interviewed at work. Those off work because of illness or injury were visited in their homes.

Members of the Bedford miners' families and of the families included in the random sample of Leigh were interviewed in the first place by the medico-social worker or her assistant, and if found to complain of rheumatic pain or any doubtful pain in the back or limbs, were then seen by the physician of the Walkden clinic or some other member of the staff of the Rheumatism Research Centre. Before these visits were started, however, it was considered advisable that the credentials of the survey and the objects to be achieved should be

known to the people of Leigh. This was done by publicity in the press and the survey was also mentioned in a broadcast on the subject of rheumatism. An approach was also made to the medical profession through the local branch of the B.M.A. In addition, an explanatory letter was sent to the head of each family to be interviewed and an appointment arranged. A home visit followed and an appointment could then be made to see members of the family who were out. All were seen personally; in no instance was reliance placed on the information of others.

Questionnaire.—The questions on rheumatic complaints were based on the preceding five-year-period (1945–1949). This period was chosen for two reasons. It covered the time during which the Essential Works Order was in operation. Under this Order all men leaving the mining industry for reasons of ill-health had to be examined by a medical referee so that records were available to assess wastage from rheumatism. The second advantage was that, as the beginning of the period coincided with the end of the war, it offered a useful aid to memory for persons interviewed.

A standard questionnaire was adopted for all initial interviews whether by the medico-social worker or by the physician. Each person was asked if he or she had, during the past five years, suffered from rheumatism, or from lumbago, sciatica, fibrositis, arthritis, neuritis, or any other aches and pains. If a positive answer was obtained the following information was also collected : the site of pain, its duration and severity as judged by loss of working time. In addition all persons were asked about their working conditions. The occupation of the individual was noted in three categories : (1) predominant work, (2) work at the onset of rheumatism, (3) present work. The duration of the predominant work was ascertained and, in the case of miners, the duration of work underground and at the coal face. The number of changes of work was also noted. Questions were asked about stresses and strains at work, position at work, heavy lifting, or the repeated use of a single joint or muscle group. Miners were questioned about the duration of their work in (*a*) a kneeling and (*b*) a stooping position, and they were asked the average distance walked underground. Details of exposure to damp and cold at work were asked of all persons together with the duration of exposure to wet conditions. Lastly any history of injury was inquired into and also any family history of rheumatic complaints. In addition, an assessment of dampness in the houses was provided by the Council inspector.

Diagnostic Problems.—Clinical examination was limited to those giving a history of rheumatic pain. The term " rheumatic pain " has been used in its widest sense to include all pain in the back and limbs not due to recent injury or unaccustomed exercise, or to acute infection or other non-rheumatic disease.

Unfortunately the diagnostic criteria for most rheumatic diseases are not clearly defined. The more advanced stages of diseases such as rheumatoid arthritis, ankylosing spondylitis, and osteo-arthritis can be recognized with some certainty, but the large variety of more transient painful syndromes which are usually called " fibrositis," " neuritis," " lumbago " are less certain both as to diagnostic criteria and to basic pathological changes. Where the history and physical signs were definite enough for a diagnosis, such as rheumatoid or osteo-arthritis, to be made with reasonable confidence, this was recorded as the cause of pain, but where the diagnosis was uncertain, the cause of pain was given as " undetermined," thus avoiding such terms as " lumbago " and " fibrositis."

During the past decade much attention has been given to disorders of the intervertebral discs, and it has become fashionable to attribute certain types of brachial, sciatic, and back pain to prolapse or degenerative changes in these discs. Though it must be admitted that the diagnosis in these cases is usually somewhat uncertain, it was felt that an attempt should be made to separate these conditions from the mass of painful disorders of undetermined nature. A category for disc disorders has therefore been included. Only a few of those placed in this category were considered to have had a definite disc prolapse. The majority were of the type having a history of recurrent low back pain, and many would formerly have been classified as osteo-arthritis of the spine or spondylosis. We shall return to the question of nomenclature in degenerative spinal disease in the second part of this study.

A number of other diagnostic categories, e.g., osteo-chondritis, gout, synovitis, and fat hernia, was included in this survey of rheumatism. Where the pain was considered to result from an obvious neurosis it was recorded as such.

As those without complaint of pain were not examined, no information on asymptomatic forms of arthritis was obtained from this part of the survey which was concerned purely with rheumatic complaints. This aspect will also be dealt with in the second part of this study.

Memory of Absence from Work.—A survey such as this, based as it is so largely on the informant's memory, is subject to considerable inaccuracy.

The inaccuracies involved in memory, even of recent illness, have been shown clearly by Stocks (1949) in his analysis of "Sickness in the Population of England and Wales in 1944–1947". In this survey sickness rates were always found to be higher for the month just completed than for previous months, so that it was evident that even an illness which had occurred two months earlier was incompletely recalled.

To check on this question of memory in relation to loss of working time a brief survey was carried out amongst the male workers in a nearby factory where accurate sickness records were available. Of 53 men who had lost work because of rheumatic complaints during the previous five years, 28 (53%) remembered correctly their lost time from rheumatism. Omitting those who were off work for less than one week and classifying the remainder into those losing one to 12 weeks and those losing more than 12 weeks as in the survey, it was found that of 41 in the first category only 25 remembered correctly, but that all three in the second category remembered correctly.

Whether a survey so widely publicized as our main surveys at Walkden and Leigh is subject to the same degree of error is uncertain. It might be expected that where informants have had ample time to turn the matter over in their minds beforehand their replies would be more accurate, but evidence from replies at a second interview of 195 Bedford and Walkden workers, of whom 15 remembered rheumatic complaints which they had previously failed to mention, indicates that some at least of the rheumatic complaints had been forgotten. The validity of comparisons between groups of workers must therefore depend, except in the case of those causing prolonged incapacity, on a similar "proneness to remember" in each group. Evidence for such a similarity will be found in the studies on complaint rate and incapacity rate in the second part of this study. Other sources of error due to sampling and observer-bias are discussed in Appendix 2.

Completeness of the Survey.—At the Bedford Colliery and at Walkden cooperation was excellent. Only one man at the Colliery and eight office workers refused to be interviewed. At the Walkden yard there were no refusals. This part of the survey is thus 99% complete. The unit used in the Leigh and families' surveys was the household, and, as far as households are concerned, these surveys are 98% complete, all but 59 of the possible 2,300 households having been included. The reasons for exclusion of the 59 households are as follows :

Refusal to help in the survey	35
Unable to trace address (families' survey) ..	14
Illness of only other in family besides miner ..	3
House empty or pulled down (Leigh survey) ..	4
Not residential (Leigh survey)	3
	59

In addition, in 49 instances one member of a family refused to cooperate or had to be given up after seven or eight unsuccessful visits, and 12 were not interviewed owing to illness, the total amounting to 1% of those who should have been seen. The response was somewhat less good to requests for permission to arrange for doctors' visits. There were 27 refusals amongst the men and 50 amongst the women, and altogether 132 persons who should have been seen by the doctor were not seen for the following reasons :

	Males	*Females*
Refusal to see the doctor	27	50
Left address or died before doctor's visit	9	16
Given up after repeated visits ..	14	12
Ill	2	—
Unable to see because of work hours	2	—
	54	78

It is considered, however, that the proportion of refusals is not such as to interfere with the validity of the results.

Results

Total Rheumatic Complaints.—The incidence of rheumatic complaints as a whole is shown in Fig. 1. As rheumatic complaints are largely a factor of age and the age distribution is not identical in miners and non-miners, each decade is considered separately.

In males the incidence of rheumatic complaints shows no great difference between miners and non-miners. Only in the fourth decade do the miners complain of substantially more rheumatic pain. The difference is statistically significant, and some explanation for it must be sought. The most probable is that there is an earlier onset in miners of some form of rheumatism which does not normally make its appearance till after the age of 40. This will be further discussed when the site of pain and diagnosis have been considered.

The females as a whole show an incidence of rheumatic complaints in all age groups closely similar to that encountered in the non-mining males. When, however, women from mining and non-mining families are compared, striking differences are found. At all ages the incidence of rheumatic complaints is lower in the females from mining families, and in the fourth decade it is halved, a

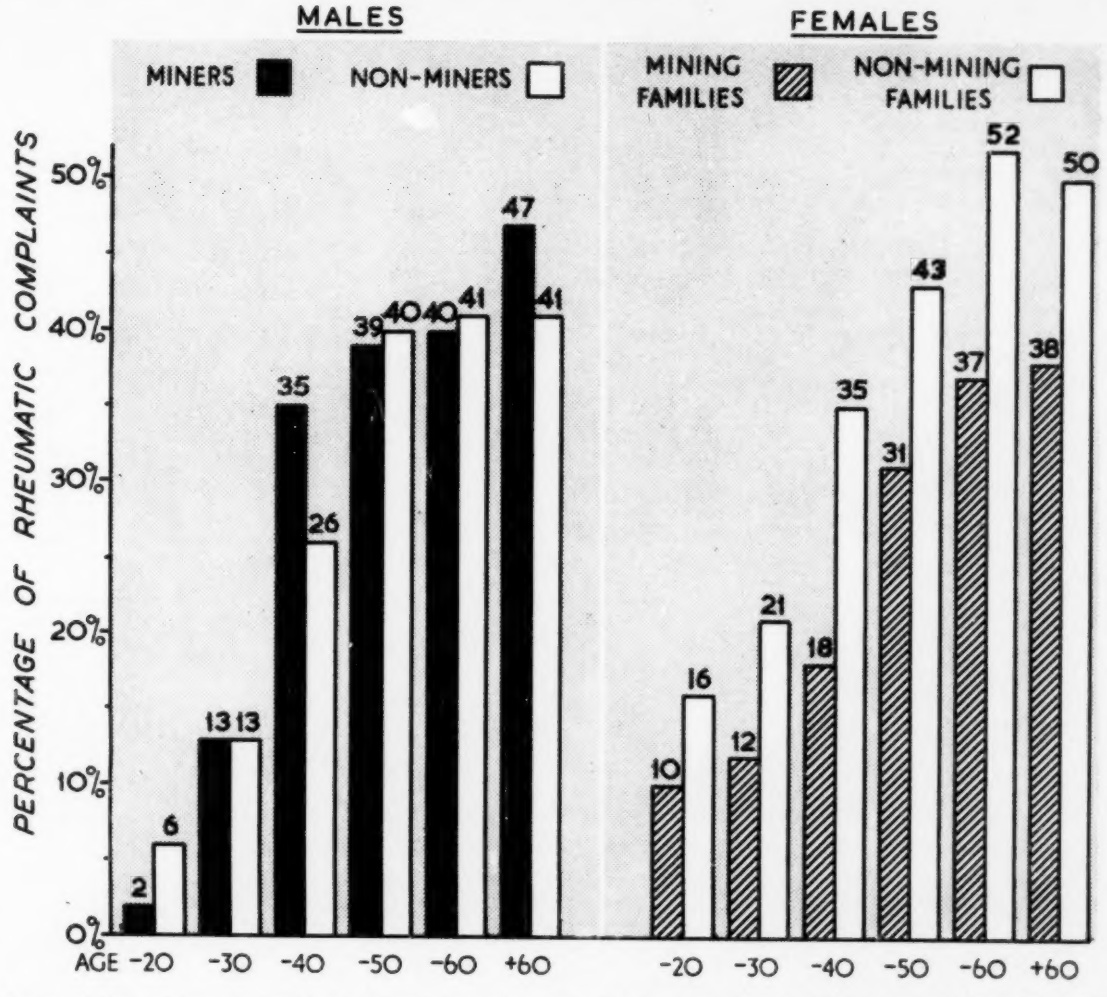
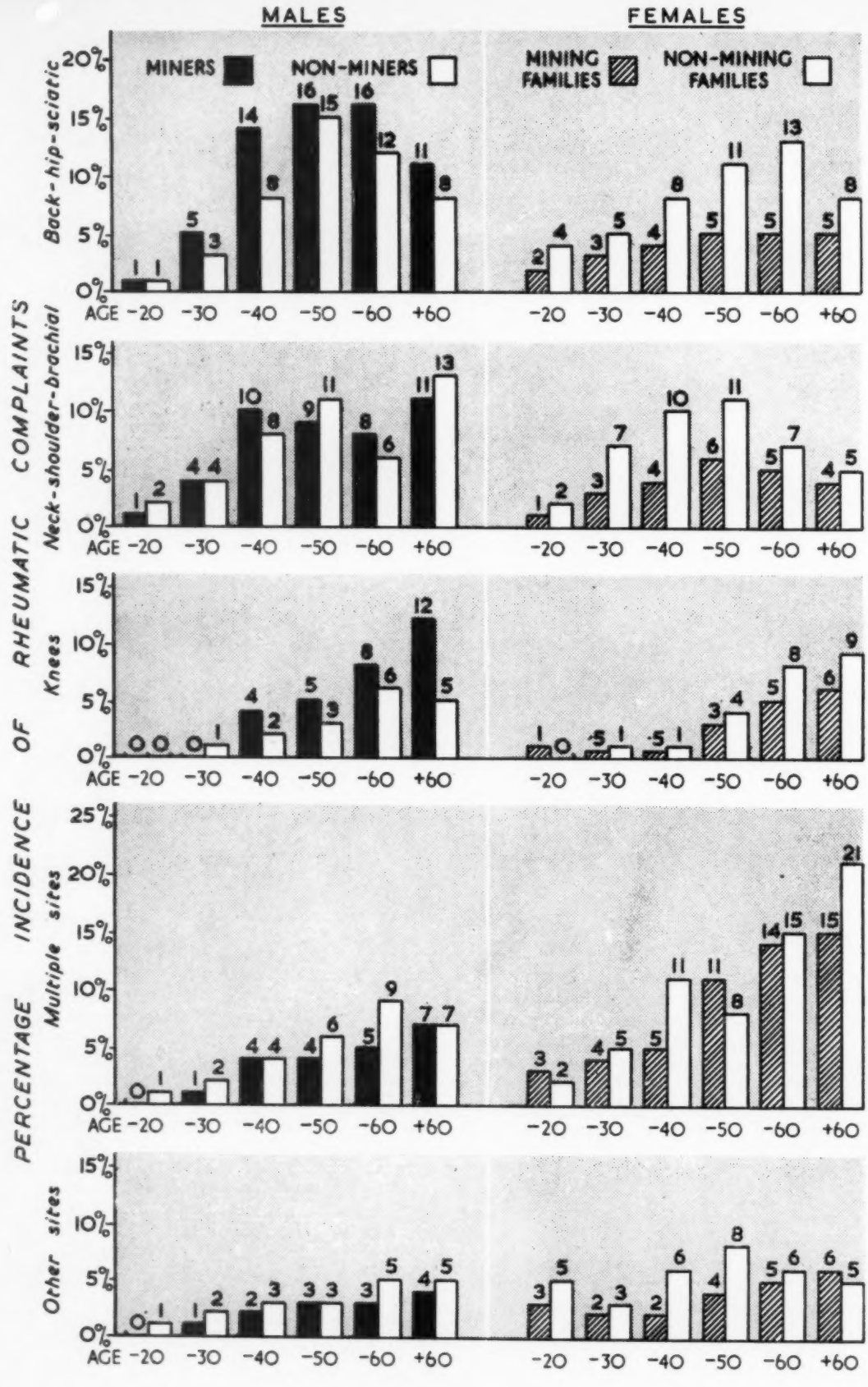


FIG. 1.—Incidence of rheumatic complaints in miners and non-miners and in the female members of mining and non-mining families. (The data upon which this figure is based are given in Appendix 1, Tables A and B. Figures above columns are the exact percentages.)

highly significant difference. This low incidence in mining families is not confined to females. In Table 1 the male non-miners are divided into those from mining and non-mining families where information on this point is available. As in the case of females there is a lower incidence at all ages in the mining families, but particularly in the fourth decade. This difference between mining and non-mining families is one of the most interesting and significant of our findings.

Site of Pain.—Sites of pain have been grouped into five general classifications designed to bring out the points of importance and at the same time to give figures of sufficient magnitude to permit of statistical study. Thus sites to which pain is referred from the lower spine and pelvic girdle are grouped together, as are sites of reference from the upper spine and shoulder girdle. The knees are considered separately, as they are likely to be of particular importance in miners. In the next part multiple sites are shown, and finally those other sites, for example, the elbows, wrists, fingers, ankles and feet, whose numerical or other importance does not warrant separate classification. The results are given in Fig. 2.

In males pain is most frequently encountered in the back-hip-sciatic distribution and this site is more prominently affected in miners than in other males. This preponderance in miners is found at all ages


MALES
FEMALES
MINERS
NON-MINERS
MINING FAMILIES
NON-MINING FAMILIES
PERCENTAGE INCIDENCE OF RHEUMATIC COMPLAINTS
Back-hip-sciatic
Neck-shoulder-brachial
Knees
Multiple sites
Other sites
AGE -20 -30 -40 -50 -60 +60

FIG

TABLE 1

INCIDENCE OF RHEUMATIC COMPLAINTS IN MALE NON-MINERS IN 1945–49

Age Group	Mining Families			Non-mining Families		
	Rheumatic			Rheumatic		
	Total	No.		Total	No.	
15—19	118	4	7%	51	3	11%
20—29	191	17		117	16	
30—39	58	5	15%ss	134	42	37%ss
40—49	30	8		160	67	
50—59	25	9	35%	92	38	42%
60+	18	6		124	53	
Total	440	49		678	219	

SS = $0{\cdot}01 > P > 0{\cdot}001$.

except the under-20s but is most marked in the fourth decade. Indeed it is to pain in this site that the high incidence of rheumatic complaints in miners at this age is largely due.

Next in frequency, the neck-shoulder-brachial pain shows a similar incidence in miners and non-miners. Other sites of pain are very much less common but pain in the knees is more frequent in miners.

In females multiple pain is a more frequent complaint than pain at a single site, neck-shoulder-brachial pain coming second, and low-back-sciatic third. All sites of pain occur with greater frequency in females from non-mining families, and in the discrepancy already noted at the fourth decade all sites participate.

In both males and females pain in the knees is uncommon except in the older age groups, and it is in these older age groups that the difference in knee pain between miners and non-miners and between mining and non-mining families is encountered.

It may thus be concluded that males suffer chiefly from low-back-sciatic pain and females from multiple pain, and that in miners there is an even greater preponderance of back-sciatic pain than in other males.

Diagnosis.—Data on diagnosis are shown in Fig. 3. Of the defined disorders, those affecting the intervertebral discs predominate in males and particularly in miners who show a higher incidence at all age groups. Between the ages of 30 and 60 disc disorders were twice as common in the mining group. Next in frequency comes osteo-arthritis which is also more frequent in miners and is found chiefly in those over the age of 50. Rheumatoid arthritis is not commonly encountered in the males and even less so in miners. The remaining defined disorders are too infrequent for statistical study, and have been grouped together in the last column. In a large proportion of cases the pain had to be classified as undetermined. Such pain was equally distributed between miners and non-miners, and showed a maximum incidence in the fourth and fifth decades.

Amongst the females osteo-arthritis was the most frequently diagnosed of the defined rheumatic disorders. As in males it was encountered chiefly in those over the age of 50, and was slightly more common in those from non-mining families. Rheumatoid arthritis was very much more frequent in females than in males, but disc disorders were comparatively uncommon and seldom encountered in females from mining families. As in males the undetermined group was the largest, and here the discrepancy between those from mining and non-mining families was highly significant, largely accounting for the difference already noted for rheumatism as a whole. As in males the highest incidence is between the ages of 30 and 50. It may be concluded therefore that in females from mining families there is a lower incidence of undetermined pain and pain due to disc degeneration and osteo-arthritis.

Incapacity.—Incapacity rates from rheumatism have been classified in two grades, those losing one week or more and those losing over three months in the five-year-period under review. These are shown in Tables 2 and 3 respectively. Apart from the under-20s more miners stated that they had lost working time from rheumatic complaints at all age groups and particularly in the fourth decade in which there were twice as many. The differences were particularly marked amongst those losing three months or more and in the fourth, fifth, and sixth decades were highly significant. The marked differences in incidence of rheumatic complaints between mining and non-mining families are not reflected in the incapacity rates, and indeed there is a greater proportion with the more prolonged disabilities in those from mining families. It would thus appear that the differences between mining and non-mining families are concerned rather with the tendency to complain than with the extent of incapacitating rheumatic disease.

Those losing three months or more have been further studied as regards site of pain and diagnosis (Tables 4 and 5), and it is clear that pain in the

FIG. 2.—Incidence of rheumatic complaints in various sites in miners and non-miners and the female members of mining and non-mining families. (The data on which this figure is based are given in Appendix 1, Tables C and D. Figures above columns are the exact percentages.)

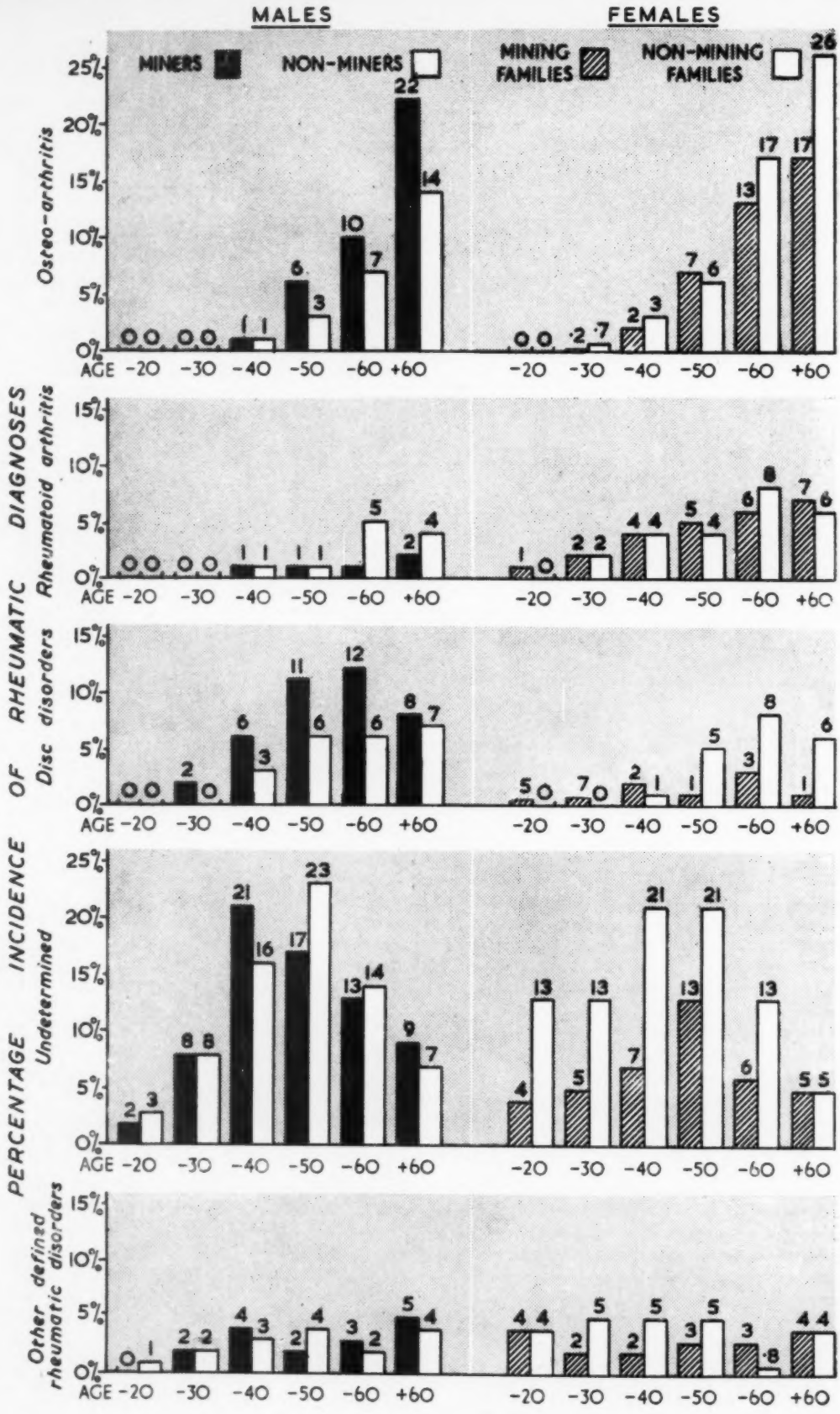

MALES
FEMALES
MINERS
NON-MINERS
MINING FAMILIES
NON-MINING FAMILIES
PERCENTAGE INCIDENCE OF RHEUMATIC DIAGNOSES
Osteo-arthritis
Rheumatoid arthritis
Disc disorders
Undetermined
Other defined rheumatic disorders
AGE -20 -30 -40 -50 -60 +60

TABLE 2

PERCENTAGE OF MINERS AND NON-MINERS ABSENT ONE WEEK OR MORE WITH RHEUMATIC COMPLAINTS IN 1945–49

Age Group	Miners			Non-miners											
	Total Miners			Mining Families			Non-mining Families			Walkden Yard, Offices and Other			Total Non-miners		
	Total	No.	%	Total	No.	%	Total	No.	%	Total	No.	%	Total	No.	%
15–19 ..	99	1	1	118	3	3	51	0	0	108	1	0·9	277	4	1
20–29 ..	367	17	5	191	9	5	117	3	3	230	9	4	538	21	4
30–39 ..	302	45[S]	15	58	2	3	134	11	8	168	15	9	360	28[S]	8
40–49 ..	429	77	18	30	3	10	160	22	14	158	22	14	348	47	14
50–59 ..	310	59	19	25	5	20	92	12	13	100	10	10	217	27	12
60+ ..	235	31	13	18	1	6	124	15	12	49	3	6	191	19	10
Total ..	1,742	230	—	440	23	—	678	63	—	813	60	—	1,931	146	—

S = 0·02 > P > 0·01

TABLE 3

PERCENTAGE OF MINERS AND NON-MINERS ABSENT THREE MONTHS OR MORE WITH RHEUMATIC COMPLAINTS IN 1945–49

Age Group	Miners			Non-miners											
	Total Miners			Mining Families			Non-mining Families			Walkden Yard Offices and Other			Total Non-miners		
	Total	No.	%	Total	No.	%	Total	No.	%	Total	No.	%	Total	No.	%
15–19 ..	99	0	0	118	1	1	51	0	0	108	1	0·9	277	2	1
20–29 ..	367	4	1	191	2	1	117	1	1	230	0	0	538	3	1
30–39 ..	302	18[SS]	6	58	2	3	134	2	1	168	3	2	360	7[SS]	2
40–49 ..	429	31[SS]	7	30	0	0	160	6	4	158	4	3	348	10[SS]	3
50–59 ..	310	26[SS]	8	25	2	8	92	1	1	100	3	3	217	6[SS]	3
60+ ..	235	17	7	18	1	6	124	6	5	49	2	4	191	9	5
Total ..	1,742	96	—	440	8	—	678	16	—	813	13	—	1,931	37	—

SS = 0·01 > P > 0·001

back-sciatic distribution is mainly responsible for the more prolonged forms of incapacity in miners. The diagnosis of disc degeneration figures largely in this group. In non-miners there is not the same preponderance of back-sciatic pain, multiple sites being almost as frequent, and diagnostically non-miners fall most commonly into the undetermined group.

Invaliding.—In the Manchester area during the five year period 1945 to 1949 rheumatism was second only to chest conditions as a cause of invaliding from the mines, and was more important than injury. In those over 60 years of age it shared top place with heart disease. Between the ages of 30 and 50 it occupied second place and in the younger age groups it was a relatively rare cause of invaliding (Appendix 1, Table G).

The rheumatic causes of invaliding have been analysed by site of pain (Appendix 1, Table H). The sites of pain are similar to those already encountered as causes of prolonged incapacity, low-back-sciatic pain predominating. The unclassified group—elbows, wrists, hands, and feet—has, however, come

FIG. 3.—Incidence of rheumatic complaints by diagnosis in miners and non-miners and female members of mining and non-mining families. (The data on which this figure is based are given in Appendix 1, Tables E and F. Figures above columns are the exact percentages.)

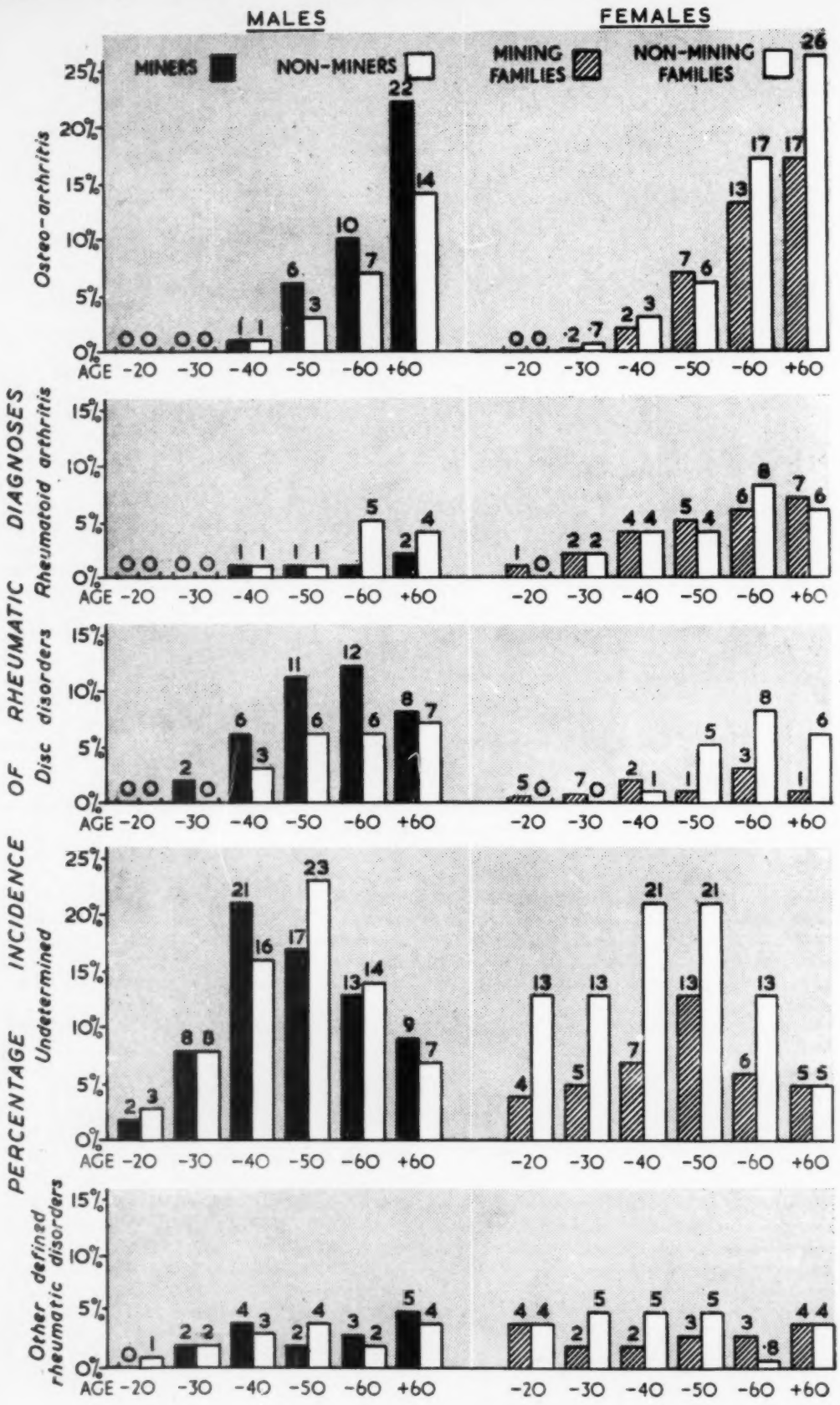

MALES
FEMALES
MINERS
NON-MINERS
MINING FAMILIES
NON-MINING FAMILIES
PERCENTAGE INCIDENCE OF RHEUMATIC DIAGNOSES
Osteo-arthritis
Rheumatoid arthritis
Disc disorders
Undetermined
Other defined rheumatic disorders
AGE -20 -30 -40 -50 -60 +60

TABLE 2

PERCENTAGE OF MINERS AND NON-MINERS ABSENT ONE WEEK OR MORE WITH RHEUMATIC COMPLAINTS IN 1945–49

Age Group	Miners			Non-miners											
	Total Miners			Mining Families			Non-mining Families			Walkden Yard, Offices and Other			Total Non-miners		
	Total	No.	%	Total	No.	%	Total	No.	%	Total	No.	%	Total	No.	%
15–19 ..	99	1	1	118	3	3	51	0	0	108	1	0·9	277	4	1
20–29 ..	367	17	5	191	9	5	117	3	3	230	9	4	538	21	4
30–39 ..	302	45[S]	15	58	2	3	134	11	8	168	15	9	360	28[S]	8
40–49 ..	429	77	18	30	3	10	160	22	14	158	22	14	348	47	14
50–59 ..	310	59	19	25	5	20	92	12	13	100	10	10	217	27	12
60+ ..	235	31	13	18	1	6	124	15	12	49	3	6	191	19	10
Total ..	1,742	230	—	440	23	—	678	63	—	813	60	—	1,931	146	—

S = 0·02 > P > 0·01

TABLE 3

PERCENTAGE OF MINERS AND NON-MINERS ABSENT THREE MONTHS OR MORE WITH RHEUMATIC COMPLAINTS IN 1945–49

Age Group	Miners			Non-miners											
	Total Miners			Mining Families			Non-mining Families			Walkden Yard Offices and Other			Total Non-miners		
	Total	No.	%	Total	No.	%	Total	No.	%	Total	No.	%	Total	No.	%
15–19 ..	99	0	0	118	1	1	51	0	0	108	1	0·9	277	2	1
20–29 ..	367	4	1	191	2	1	117	1	1	230	0	0	538	3	1
30–39 ..	302	18[SS]	6	58	2	3	134	2	1	168	3	2	360	7[SS]	2
40–49 ..	429	31[SS]	7	30	0	0	160	6	4	158	4	3	348	10[SS]	3
50–59 ..	310	26[SS]	8	25	2	8	92	1	1	100	3	3	217	6[SS]	3
60+ ..	235	17	7	18	1	6	124	6	5	49	2	4	191	9	5
Total ..	1,742	96	—	440	8	—	678	16	—	813	13	—	1,931	37	—

SS = 0·01 > P > 0·001

back-sciatic distribution is mainly responsible for the more prolonged forms of incapacity in miners. The diagnosis of disc degeneration figures largely in this group. In non-miners there is not the same preponderance of back-sciatic pain, multiple sites being almost as frequent, and diagnostically non-miners fall most commonly into the undetermined group.

Invaliding.—In the Manchester area during the five year period 1945 to 1949 rheumatism was second only to chest conditions as a cause of invaliding from the mines, and was more important than injury. In those over 60 years of age it shared top place with heart disease. Between the ages of 30 and 50 it occupied second place and in the younger age groups it was a relatively rare cause of invaliding (Appendix 1, Table G).

The rheumatic causes of invaliding have been analysed by site of pain (Appendix 1, Table H). The sites of pain are similar to those already encountered as causes of prolonged incapacity, low-back-sciatic pain predominating. The unclassified group—elbows, wrists, hands, and feet—has, however, come

FIG. 3.—Incidence of rheumatic complaints by diagnosis in miners and non-miners and female members of mining and non-mining families. (The data on which this figure is based are given in Appendix 1, Tables E and F. Figures above columns are the exact percentages.)

TABLE 4

SITE OF RHEUMATIC PAIN IN MINERS AND NON-MINERS ABSENT THREE MONTHS OR MORE IN 1945–49

Age Group	Back, Hips, and Sciatic				Neck, Shoulders, and Brachial				Knees				Multiple Sites				Other Sites			
	Miners		Non-miners		Miners		Non-miners		Miners		Non-miners		Miners		Non-miners		Miners		Non-miners	
	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%
15–19 ..	0	0	1	0·4	0	0	0	0	0	0	0	0	0	0	1	0·4	0	0	0	0
20–29 ..	2	0·5	1	0·2	1	0·3	0	0	0	0	0	0	1	0·3	1	0·2	0	0	0	0
30–39 ..	9	3	3	0·8	4	1	1	0·3	2	0·7	2	0·6	3	1	1	0·3	0	0	0	0
40–49 ..	14	3	5	1	6	1	1	0·3	6	1	1	0·3	5	1	2	0·6	0	0	0	0
50–59 ..	14	5	2	0·9	5	2	0	0	2	0·6	0	0	5	2	2	0·9	0	0	1	0·5
60+ ..	3	1	3	2	1	0·4	0	0	6	3	1	0·5	6	3	4	2	0	0	1	0·5
Total ..	42	—	15	—	17	—	2	—	16	—	4	—	20	—	11	—	0	—	2	—

TABLE 5

DIAGNOSIS IN MINERS AND NON-MINERS ABSENT THREE MONTHS OR MORE WITH RHEUMATIC COMPLAINTS IN 1945–49

Age Group	Osteoarthritis				Rheumatoid Arthritis				Disc Disorders				Undetermined				Other Defined Rheumatic Disorders			
	Miners		Non-miners		Miners		Non-miners		Miners		Non-miners		Miners		Non-miners		Miners		Non-miners	
	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%
15–19 ..	0	0	0	0	0	0	0	0	0	0	1	0·4	0	0	0	0	0	0	1	0·4
20–29 ..	0	0	0	0	0	0	1	0·2	0	0	1	0·2	2	0·5	2	0·4	1	0·3	0	0
30–39 ..	0	0	1	0·3	2	0·7	0	0	7	2	1	0·3	7	2	2	0·6	1	0·3	2	0·6
40–49 ..	6	1	1	0·3	2	0·5	0	0	12	3	2	0·6	6	1	4	1	4	0·9	2	0·6
50–59 ..	3	1	2	0·9	1	0·3	1	0·5	11	4	0	0	8	3	2	0·9	3	1	0	0
60+ ..	8	3	3	2	1	0·4	2	1	3	1	0	0	1	0·4	1	0·5	4	2	1	0·5
Total ..	17	—	7	—	6	—	4	—	33	—	5	—	24	—	11	—	13	—	6	—

to occupy a more prominent place. Diagnoses were given on the discharge note, i.e., the diagnoses of the medical referee submitting the patient for discharge. Most were described as fibrositis or simply as rheumatism and there was a large proportion of arthritis (unspecified). The large proportion of cases with an ill-defined diagnosis rendered any comparison with our findings of doubtful value.

It should be pointed out that these data for invaliding refer to the miners in the Manchester area as a whole, and not only to those mines situated in Leigh which were included in the survey. In all, there are 22 mines in the area, and they employ some 25,000 workers, so that the actual invaliding rate from rheumatism for the five-year period averages only eight men per colliery or seven per 1,000 men employed.

Comparison with Other Forms of Illness.—The data for invaliding were obtained from the records of the Ministry of Fuel and Power. In addition it has been possible to consult records of a sick

benefit society at the Parsonage Colliery in Leigh. These show that incapacitating illness is of a similar type to that requiring invaliding from the mines. Chest disease heads the list and rheumatism is the second most important cause of incapacity. This is followed in turn by digestive disorders and upper respiratory infections. Data have not been obtained for incapacity due to compensatable injury. There can be little doubt that such data were they available would include many instances falling within our classification of " rheumatic complaints ", arising from, and justifiably attributed to injury.

Discussion

From the data presented it is clear that rheumatic complaints are of frequent occurrence in the population, and that in miners the gross incidence of such complaints is no greater than in the population as a whole. The degree of incapacity, on the other hand, appears greater in miners as shown by statements on loss of working time, and there is evidence of an earlier onset of symptoms as shown by a steeper rise in incidence at the fourth decade.

The more prolonged forms of incapacity are associated for the most part with pain in the low-back-sciatic distribution, but neck-shoulder-brachial and knee pain are also in part responsible for the increased incapacity in miners. Diagnostically there is a predominance of disc degeneration in miners in this group as indeed also in those with lesser grades of incapacity. Osteo-arthritis and undetermined pain are also in part responsible for the increased incapacity rate in miners. When the age groups are studied separately it is seen that low-back-sciatic pain of undetermined origin or due to disc degeneration is mainly responsible for incapacity between the ages of 30 and 60, and pain in the knees due to osteo-arthritis in those over 60 years of age.

Before discussing these points further it is necessary to consider the difference between disc degeneration and " pain undetermined ". The tendency was to place the case in the undetermined group if there had been only one attack of pain and no residual physical signs, and into the degenerative group if there had been a history of repeated attacks and if limitation of certain movements of the spine had persisted. Symptoms and signs of prolapse of the nucleus pulposus would also determine that the case be included in this category, though these constitute only a small proportion of the disc disorders. Thus it is likely that at least a proportion of those classed as undetermined were in reality early cases of disc degeneration. This point will be further studied in a later paper.

The fourth decade is of particular importance in this study, as it is this age group which shows an all-round increase of rheumatic complaints in miners. Before this age the miners show a diminished incidence, and in the older age groups there is no significant difference between miners and non-miners. This has been interpreted as indicating an earlier onset of some form of rheumatism normally arising about the fifth decade. It remains to determine the nature of this form of rheumatism. Comparison of the miners and non-miners in this age group indicates that the pain is predominantly in the low-back-sciatic distribution, and that it is those rheumatic complaints which have been diagnosed as disc degeneration which are mainly responsible for the discrepancy between miners and non-miners in this age group. If disc degeneration does, in fact, arise in the fifth decade in males in the general population, an earlier onset of this disease in the lower dorsal and lumbar spine in miners would explain our findings. According to Schmorl and Junghanns (1932) routine post-mortem studies of spines have shown that in males the condition commonly makes its appearance in the fifth decade. In females it appears a decade later. Thus, as far as this preliminary survey goes, it points to both an earlier onset of and greater incapacity from lower dorsal and lumbar disc degeneration as the main feature of rheumatism in miners. Whether the greater incapacity in miners is due to more severe disease or to the nature of their work must await the results of the radiological studies.

It remains only to explain the findings in the miners' families. This part of the survey was designed originally to exclude hereditary and home environmental factors as a cause of any increased incidence which might be found in miners. Though male relatives of miners were too few for a detailed study of hereditary factors as such, there is fairly convincing evidence against either an environmental or hereditary factor in the rheumatism of miners. In fact the miners' families had, at all ages, fewer complaints than members of non-mining families. Whether they have less rheumatic disease this survey does not demonstrate, though this is not so improbable as might appear, for mining is essentially a family occupation, some 90% of miners coming of mining stock. Families prone to rheumatism would not tend to favour so heavy an occupation, and those following it would be rapidly weeded out. This would not, however, explain the low incidence in the wives, who comprise the largest proportion of the females in the mining families. Only some 50% of these are of mining stock, a proportion similar to that obtaining in the

local population of Leigh. A more probable explanation is to be found in an altered base-line of normality. Most people have an aching muscle or joint occasionally, but may or may not regard this as abnormal, or worth mentioning in a survey of rheumatic pains. In a family, one of whose members has lost a considerable amount of work from rheumatism, the boundary between normal and abnormal will tend to be relatively higher, as the other members of the family will feel their own complaints to be relatively insignificant. This explanation is supported by the lower incidence in members of mining families of those forms of rheumatism not giving rise to loss of working time, and of those vague rheumatic pains classified as undetermined. Another pointer is that the discrepancy is greatest in the fourth decade when miners are beginning to lose work because of rheumatic complaints; in fact the rheumatic complaints in mining families may be described as a "mirror-image" of the miners' rheumatism. It would be interesting to know whether a similar effect is to be found in the families of other workers prone to rheumatism.

We have not considered a possible beneficial effect from home environment, though this may be a factor. The miners in Lancashire were at the time of the survey receiving an extra hundredweight of coal a month, and besides, the higher rates of pay of miners might result in better food. To what extent these factors might affect the incidence of rheumatic complaints is uncertain, but we venture to think them less important than the factors mentioned above.

Summary

An investigation has been made into the incidence of rheumatic complaints in miners by means of a field survey arranged to include control groups of non-mining males and of females from mining and non-mining families.

The gross incidence of rheumatic complaints was not found to be appreciably different in miners and non-miners, but there was evidence of an earlier onset in miners, as shown by a higher incidence in the fourth decade.

The miners' statements indicated that they lost more working time from rheumatic complaints than non-miners.

Rheumatic pain in miners was chiefly in the lumbar and sciatic distribution, and pain in these sites was largely accounted for by the increased incidence of rheumatic complaints in the fourth decade and for the increased loss of working time in miners. Miners also showed an increased incidence of knee pain.

Tentative diagnoses made in the field indicated that the lumbar sciatic pain may frequently result from disorders of the intervertebral discs. There was also evidence of an increased incidence of osteo-arthritis in the miners. Confirmation of these findings will be the subject of a further paper.

A study of invaliding records made under the Essential Works Order showed that invaliding from the mines was due most commonly to chest conditions, rheumatism coming second in importance. Those invalided for rheumatism complained chiefly of low-back sciatic pain.

The incidence of rheumatic complaints in members of the miners' families was lower than in the general populations and considerably lower than in miners.

This work was carried out under a research grant from the Miners' Welfare Commission to whom we are grateful for permission to publish.

References

Davidson, L. S. P., and Duthie, J. R. (1937). Quoted in "Chronic Rheumatic Diseases", 1945, p. 7–8.

Horder, Lord (1944). Rheumatism . . . A Plan for National Action. 4th Edit. London.

Kahlmeter (1923). Quoted in "Chronic Rheumatic Diseases", 1945 p. 7.

Newman, G., ed. (1924). Reports on Public Health and Medical Subjects, No. 23. H.M.S.O., London.

Schmorl, G., and Junghanns, H. (1932). Die gesunde und kranke Wirbelsaüle im Röntgenbild, Leipzig.

Scotland. Department of Health (1932–1937). Annual "Reports on Incapacitating Sickness", 1930–1936. H.M.S.O., Edinburgh.

——, (1945). "Chronic Rheumatic Diseases." H.M.S.O., Edinburgh.

Stocks, P. (1949). "Sickness in the Population of England and Wales in 1944–1947." H.M.S.O., London.

APPENDIX 1

TABLE A

INCIDENCE OF RHEUMATIC COMPLAINTS IN MINERS AND MALE NON-MINERS IN 1945–49

Age Group	Miners			Non-Miners		
	Leigh, Bedford, and Family Surveys			Leigh, Walkden, and Family Surveys		
	Total	Rheumatic		Total	Rheumatic	
		No.	%		No.	%
15—19	99	2	2	277	16	6
20—29	367	47	13	538	69	13
30—39	302	105s	35	360	93s	26
40—49	429	165	39	348	140	40
50—59	310	124	40	217	88	41
60+	235	111	47	191	81	41
Total	1,742	554	—	1,931	487	—

S = 0·05 < P > 0·02.

TABLE B

INCIDENCE OF RHEUMATIC COMPLAINTS IN FEMALES IN MINING AND NON-MINING FAMILIES IN 1945–49

Age Group	Mining Families			Non-Mining Families			Family Status Unknown	
	Total	Rheumatic		Total	Rheumatic		Total	Rheumatic
		No.	%		No.	%		
15—19	219	22	10	55	9	16	11	0
20—29	433	50[s]	12	154	32[s]	21	42	6
30—39	321	57[ss]	18	168	59[ss]	35	58	17
40—49	400	124[s]	31	171	74[s]	43	52	19
50—59	331	122[s]	37	133	69[s]	52	48	21
60+	231	88	38	141	71	50	117	60
Total	1,935	463	—	822	314	—	328	123

S = 0·05 < P > 0·02.
SS = P < 0·01.

TABLE C

ANALYSIS OF RHEUMATIC COMPLAINTS BY SITE OF PAIN IN MALES IN 1945–49

Age Group	Back, Hips, and Sciatic						Neck, Shoulders, and Brachial						Knees						Multiple Sites						Other Sites					
	Miners		Non-Miners		Total Males		Miners		Non-Miners		Total Males		Miners		Non-Miners		Total Males		Miners		Non-Miners		Total Males		Miners		Non-Miners		Total Males	
	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%
15–19 ..	1	1	4	1	5	1	1	1	6	2	7	2	0	0	0	0	0	0	0	0	3	1	3	1	0	0	2	1	2	1
20–29 ..	20	5	18	3	38	4	16	4	20	4	36	4	1	0·3	6	1	7	1	3	1	12	2	15	2	3	1	9	2	12	1
30–39 ..	42[S]	14	28[S]	8	70	11	31	10	29	8	60	9	11	4	8	2	19	3	12	4	13	4	25	4	7	2	9	3	16	2
40–49 ..	69	16	51	15	120	15	39	9	37	11	76	10	21	5	12	3	33	4	19	4	21	6	40	5	14	3	9	3	23	3
50–59 ..	51	16	25	12	76	14	24	8	12	6	36	7	24	8	13	6	37	7	14[S]	5	20[S]	9	34	6	8	3	10	5	18	3
60+ ..	26	11	16	8	42	10	26	11	24	13	50	12	28[S]	12	10[S]	5	38	9	17	7	14	7	31	7	10	4	10	5	20	5
Total ..	209	—	142	—	351	—	137	—	128	—	265	—	85	—	49	—	134	—	65	—	83	—	148	—	42	—	49	—	91	—

S = 0·02 > P > 0·01 S = 0·05 > P > 0·02 S = 0·05 > P > 0·02

TABLE D

ANALYSIS OF RHEUMATIC COMPLAINTS BY SITE OF PAIN IN FEMALES IN 1945–49

Age Group	Back, Hips, and Sciatic						Neck, Shoulders, and Brachial						Knees						Multiple Sites						Other Sites					
	Mining		Non-Mining		Total Females		Mining		Non-Mining		Total Females		Mining		Non-Mining		Total Females		Mining		Non-Mining		Total Females		Mining		Non-Mining		Total Females	
	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%
15–19 ..	4	2	2	4	6	2	3	1	1	2	4	1	3	1	0	0	3	1	6	3	1	2	7	2	6	3	3	5	9	3
20–29 ..	11	3	8	5	19	3	12[S]	3	11[S]	7	25	4	2	0·5	2	1	5	0·8	16	4	7	5	25	4	7	2	4	3	11	2
30–39 ..	13	4	13	8	28	5	14[S]	4	16	10	36	7	2	0·6	2	1	6	1	17[S]	5	18[S]	11	39	7	5[SS]	2	10[SS]	6	16	3
40–49 ..	21[S]	5	19[S]	11	43	7	25[S]	6	19[S]	11	52	8	14	3	6	4	23	4	45	11	14	8	60	10	14[S]	4	14[S]	8	30	5
50–59 ..	17[SS]	5	18[SS]	13	40	8	18	5	9	7	31	6	17	5	10	8	30	6	47	14	20	15	75	15	17	5	8	6	26	5
60+ ..	12	5	11	8	30	6	10	4	7	5	23	5	15	6	13	9	31	6	35	15	29	21	93	19	14	6	7	5	30	6
Total ..	78	—	71	—	166	—	82	—	63	—	171	—	53	—	33	—	98	—	166	—	89	—	299	—	63	—	46	—	122	—

S = 0·05 > P > 0·01 SS = P < 0·01

TABLE E

ANALYSIS OF RHEUMATIC COMPLAINTS IN MALES BY DIAGNOSIS IN 1945–49

Age Group	Osteo-Arthritis						Rheumatoid Arithritis						Disc Disorders						Undetermined						Other Defined Rheumatic Disorders					
	Miners		Non-Miners		Total Males		Miners		Non-Miners		Total Males		Miners		Non-Miners		Total Males		Miners		Non-Miners		Total Males		Miners		Non-Miners		Total Males	
	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%
15–19 ..	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	2	2	9	3	11	3	0	0	4	1	4	1
20–29 ..	1	0	1	0	2	0	2	0	2	0	4	0	6	2	2	0	8	1	28	8	43	8	71	8	6	2	12	2	18	2
30–39 ..	4	1	4	1	8	1	3	1	2	1	5	1	18	6	12	3	30	5	65	21	59	16	124	19	11	4	12	3	23	3
40–49 ..	26	6	11	3	37	5	4	1	5	1	9	1	49	11	21	6	70	9	71s	17	79s	23	150	19	9	2	14	4	23	3
50–59 ..	32	10	16	7	48	9	2	1	11	5	13	2	36	12	13	6	49	9	40	13	31	14	71	13	8	3	5	2	13	2
60+ ..	51	22	27	14	78	18	5	2	7	4	12	3	19	8	14	7	33	8	20	9	14	7	34	8	12	5	8	4	20	5
Total ..	114	—	59	—	173	—	16	—	27	—	43	—	128	—	63	—	191	—	226	—	235	—	461	—	46	—	55	—	101	—

For ages above 40,
$0{\cdot}02 > P > 0{\cdot}01$

For ages above 30,
$0{\cdot}01 > P > 0{\cdot}001$

s = $P = 0{\cdot}05$

TABLE F

ANALYSIS OF RHEUMATIC COMPLAINTS BY DIAGNOSIS IN FEMALES IN 1945–49

Age Group	Osteo-Arthritis						Rheumatoid Arthritis						Disc Disorders						Undetermined						Other Defined Rheumatic Disorders					
	Mining		Non-Mining		Total Females		Mining		Non-Mining		Total Females		Mining		Non-Mining		Total Females		Mining		Non-Mining		Total Females		Mining		Non-Mining		Total Females	
	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%	Rh.	%
15–19 ..	0	0	0	0	0	0	3	1	0	0	3	1	1	0·5	0	0	1	0·4	9s	4	7s	13	16	6	8	4	2	4	10	4
20–29 ..	1	0·2	1	0·7	2	0·3	9	2	3	2	13	2	3	0·7	0	0	3	0·5	22ss	5	22ss	14	46	7	7	2	7	5	14	2
30–39 ..	6	2	5	3	12	2	14	4	6	4	21	4	6	2	2	1	8	1	23ss	7	36ss	21	68	12	5	2	8	5	16	3
40–49 ..	29	7	10	6	41	7	20	5	7	4	28	4	5ss	1	9ss	5	16	3	50s	13	36s	21	96	15	12	3	8	5	21	3
50–59 ..	43	13	22	17	71	14	20	6	10	8	37	7	10	3	10	8	25	5	20s	6	17s	13	38	7	11	3	1	0·8	13	3
60+ ..	40	17	36	26	103	21	17	7	8	6	34	7	3ss	1	9ss	6	17	3	12	5	7	5	27	6	10	4	6	4	18	4
Total ..	119	—	74	—	229	—	83	—	34	—	136	—	28	—	30	—	70	—	136	—	125	—	291	—	53	—	32	—	92	—

S = $0{\cdot}05 > P > 0{\cdot}01$
SS = $P < 0{\cdot}01$

TABLE G

DISCHARGES FROM MINES IN NO. 1 (MANCHESTER) AREA* IN 1945–1949 BY DISABILITY AND AGE GROUP

Disability	Total Discharges		Age Groups						
	No.	Rate per 1,000 Miners in Area	15–19	20–29	30–39	40–49	50–59	60+	Age not Stated
Chest complaints ..	272	10·9	4	48	72	78	12	4	54
Rheumatism	171	6·9	2	23	55	58	6	12	15
Ulcers	129	5·2	2	30	43	33	3	0	18
Injuries	119	4·8	0	26	32	28	5	5	23
Disorders of vision ..	112	4·4	7	30	18	27	0	1	29
Skin diseases	110	4·3	7	31	22	21	10	0	19
Neurosis, etc.	103	4·1	10	35	24	10	1	0	23
Cardiac complaints ..	95	3·8	2	17	19	22	8	12	15
E.N.T. complaints ..	67	2·7	5	29	14	5	0	0	14
Hernia	47	1·9	2	11	8	11	6	5	4
Nystagmus	44	1·8	0	1	12	18	3	1	9
Disorders of C.N.S. ..	40	1·7	1	17	8	2	0	1	11
Disorders of digestive system	35	1·4	1	9	8	5	0	2	10
T.B.	33	1·3	1	12	10	3	2	0	5
Rheumatic fever† ..	8	0·4	1	4	0	2	0	0	1
Miscellaneous ..	185	7·4	5	56	36	37	9	11	31
Total	1,570	63·1	50	379	381	360	65	54	281

* Figures from the records of Ministry of Fuel and Power, Manchester. Total population, 24,854.
† Rheumatic fever has not been included with rheumatism as invaliding was for the cardiac complications.

TABLE H

SITE OF PAIN IN INVALIDING FOR RHEUMATISM 1945–1949

Age Groups	Total	Back	Neck	Knees	Multiple Sites	Other Sites	Not Given
15—19	2	0	0	0	0	1	1
20—29	23	12	1	1	0	1	8
30—39	55	22	1	3	6	9	14
40—49	58	26	3	7	3	1	18
50—59	6	0	0	0	2	0	4
60+	12	2	2	1	1	1	5
Not given	15	8	2	2	2	1	0
Total	171	70	9	14	14	14	50

APPENDIX 2

Sources of Error

In addition to problems of memory which have already been considered there are certain other sources of error which are a part of all field survey work and which must briefly be discussed.

Errors of Sampling.—These have been avoided by taking the whole population of the Bedford Colliery and of the Walkden yard and offices. Provided that these are not taken as representative of all miners and non-mining male workers no error of sampling is involved. In the town of Leigh it was impossible to study the whole population, but by the mode of sampling households it is considered that any bias has been overcome.

Observer-bias.—Where several observers are used the question of observer-bias becomes of considerable importance, particularly if there is an uneven distribution of population groups in those seen by each observer. In this survey data were collected by two social workers and five doctors. The question thus arises whether there was uniformity of procedure between these observers and to what extent there was agreement as to diagnosis amongst the latter. For non-medical interviewers the difficulty was to decide whether in any particular case the complaint should be referred to the doctors as possibly rheumatic or whether it could safely be ascribed to recent injury, operation, or unaccustomed exercise, or be a symptom of some acute infection. In this survey all doubtful cases were referred, even if slight, so that selection by the interviewers was reduced to a minimum. The salient question on rheumatic complaints was asked in the same way by all the interviewers whether medical as at the Bedford Colliery, Walkden yard and offices, or non-medical as in the Leigh and families' surveys. Comparing the incidences of rheumatic complaints in those seen by the two non-medical interviewers these were 30 and 32% respectively after non-rheumatic disorders had been excluded by the medical interviewers. Similarly a comparison of those seen initially by a social worker with those seen only by a medical interviewer shows a similar final incidence of rheumatic complaints of 29% and 26% respectively. Moreover, a comparison of results in miners and non-miners (Table X) shows that the increased incidence of knee pain and loss of working time one week plus and three months plus in miners was noted by all observers and that the increased incidence of low-back-sciatic pain in miners was noted by two observers, the third finding an identical incidence in miners and non-miners. There is thus no evidence that the results of the questionnaire were in any way influenced by an undue bias by one observer.

The diagnoses made by the five physicians taking part in the Leigh and families' surveys are shown in Table Y. As some of the physicians saw only a few and as observer 1 saw some 70% of the whole, the main problem is to find out if the diagnoses made by observer 1 were substantially different from the rest. There is a significant difference between observer 1 and the remainder only in the group of disc disorders, the former placing 16% of the cases in this category, the remainder only 8%. This group, however, is at present ill-defined when taken as a purely clinical diagnosis ; indeed, except in a few with nucleus pulposus prolapse there are no clear physical signs on which the diagnosis may be based. In the well defined disorders, rheumatoid and osteo-arthritis, there is no significant difference between observer 1 and the remainder. It may thus be concluded

TABLE X

INCIDENCE OF RHEUMATIC PAIN IN MINERS AND NON-MINERS

Observer	Category	Total	Site of Pain		Incapacity	
			Back-sciatic	Knee	1 Week or More	3 Months or More
1. Non-medical	Miners	391	76 (19%)	20 (5%)	67 (17%)	31 (8%)
	Non-miners	713	81 (11%)	16 (2%)	77 (11%)	19 (3%)
2. Non-medical	Miners	145	20 (14%)	11 (8%)	20 (14%)	11 (8%)
	Non-miners	341	35 (10%)	15 (4%)	32 (9%)	8 (2%)
3. Medical	Miners	987	118 (12%)	66 (7%)	125 (13%)	47 (5%)
	Non-miners	703	82 (12%)	31 (4%)	60 (9%)	13 (2%)

TABLE Y

DIAGNOSIS MADE BY FIVE PHYSICIANS IN LEIGH AND FAMILIES SURVEYS

Observer	Total	Osteo-arthritis	Rheumatoid Arthritis	Disc Disorders	Undetermined	Other Diagnoses
1.	906	223 (25%)	107 (12%)	141 (16%)	332 (36%)	103 (11%)
2.	218	50	39	17	72	40
3.	96	25	15	9	37	10
4.	91	21	10	5	45	10
5.	41	18	1	6	12	4
2–5	446	114 (25%)	65 (15%)	37 (8%)	166 (37%)	64 (14%)

that observer bias is not responsible for the findings of this survey relating to site of pain, loss of working time, or to the diagnoses of osteo- and rheumatoid arthritis, but that it may play a part in the relative distribution of cases between the disc disorders and the undetermined group.

Brit. J. industr. Med., 1952, **9**, 19.

A STUDY OF THE CONDITIONS UNDER WHICH METHANOL MAY EXERT A TOXIC HAZARD IN INDUSTRY

BY

G. LEAF and L. J. ZATMAN

From the Physiology Department, the University of Manchester

(RECEIVED FOR PUBLICATION AUGUST 14, 1951)

All lower aliphatic alcohols have rapid narcotic effects the degree of which, as Richardson (1869) showed, increases with molecular weight of the alcohols in the homologous series. Methanol shares with its homologues this acute narcotic action but is anomalous in that it also exerts characteristic chronic toxic effects, probably due to the slowness with which it is eliminated from the body and the toxicity of the products of its metabolic oxidation, formaldehyde and formic acid. Owing to this difference the toxic effects of methanol are more insidious than those of its homologues, and there is therefore a definite hazard associated with the now extensive industrial use of methanol. The danger is increased by the tendency to confuse methanol with ethanol and use it as a beverage. This unfortunate error has caused many serious outbreaks of poisoning in the past. McGregor (1943), Jacobson, Russell, Grimm, and Fox (1945), Kaplan and Levreault (1945), Røe (1946), and Chew, Berger, Brines, and Capron (1946) describe recent examples.

The danger from its use in industry was first noted by McFarlan in 1856 (McCord, 1931), and numerous cases of industrial poisoning have been reported since then (see von Oettingen, 1943; Hamilton, 1925; Browning, 1937, for summaries of the literature). More recently, awareness of the danger and consequent caution have greatly reduced the number of cases in spite of a great increase in the use of methanol, and with reasonable care it can be used quite safely in industry. During the recent war a rapid expansion in the use of methanol was envisaged with the corresponding danger of a renewal of the hazard (Humperdinck, 1941). The present work was therefore undertaken in order to establish accurate safety limits for exposure to methanol.

This problem had previously stimulated a certain amount of experimental work. It was early shown that exposure of rats, mice, dogs, and cats to methanol vapour may cause death (Tyson and Schoenberg, 1914; Loewy and von der Heide, 1914; Macht, 1920; Weese, 1928) and that in some cases death may be delayed until some time after termination of the exposure (Loewy and von der Heide, 1914; Witte, 1933). The conditions employed in these earlier experiments were generally rather drastic, but more carefully controlled experiments have been carried out by McCord (1931) using rats, rabbits, and monkeys, and by Yant and Schrenk (1937), Yant, Schrenk, and Sayers (1931), and Sayers, Yant, Schrenk, Chornyak, Pearce, Patty, and Linn (1944), using guinea-pigs, dogs, and monkeys. Full reports of these experiments are not available in this country, but McCord concluded that continued exposure to a vapour concentration of 1,000 p.p.m. or exposure to conditions where 31 ml. of methanol may be absorbed in 41 hours would be dangerous. Sayers and others (1944) report that exposure to 500 p.p.m. for eight hours a day or exposure to 9,000 p.p.m. for short periods (less than five minutes) eight times a day was not injurious to dogs.

McCord (1931) also demonstrated with monkeys that sufficient methanol can be absorbed through the skin to cause death. Rost and Braun (1926) and Yant and others (1931) discount the practical importance of this route of absorption, and indeed conditions akin to those used experimentally by McCord, which involved the application of methanol-soaked pads under a gas-tight cover, are hardly likely to be encountered in industrial practice.

Results obtained in experiments with animals have been used to estimate safety limits of exposure to methanol for man. It has been noted that McCord suggested that conditions where 31 ml. of methanol may be absorbed in 41 hours (18 g./24 hours) are dangerous. Widmark (1933) calculated from the determined rates of elimination of methanol

and ethanol by rabbits and ethanol by man that 34 g. of methanol could be safely eliminated in 24 hours. By similar comparison between dog and man Neymark (1936) amended this value to 14·4 g./24 hours, a result more in keeping with the findings of McCord (1931).

The application to human problems of results obtained in experiments with animals always requires caution. Laboratory animals show wide variations in sensitivity to methanol (Rost and Braun, 1926; Scott, Helz, and McCord, 1933) especially when this is inhaled as the vapour (Loewy and von der Heide, 1914; McCord, 1931). Man appears to be much more sensitive than the smaller mammals to the effects of this poison. Values for the minimum acutely lethal dose for small laboratory animals vary from 4·7 g./kg. for the cat (Macht, 1920) to 14g./kg. for the rabbit (Munch and Schwartze, 1925; Nicloux and Placet, 1912). For man the lethal dose is estimated by Røe (1943) and Poulsson (1941) as less than 1 g./kg. Data from fatalities caused by drinking methanol suggest a wide variation in individual sensitivity in man, some individuals dying after consumption of less than 30 g. (Røe, 1946; Ziegler, 1921; Egg, 1927) whilst others have consumed 150 g. without ill effect (Røe, 1946; Chew, Berger, Brines, and Capron, 1946; Uhthoff, 1915). Røe suggests that this variation is largely due to the simultaneous consumption of varying amounts of ethanol but the report of Chew and others (1946) suggests that this is not entirely so.

The safety limits quoted above must therefore be accepted with reserve in the absence of data obtained with human subjects. The aim of the present work was to obtain such data. The experiments were designed to determine the minimum conditions under which accumulation of methanol may occur, that is, conditions where the amount of methanol absorbed during a normal working period of eight hours would not be completely eliminated* before the beginning of the next working period 16 hours later. This requires a knowledge of the processes of absorption and elimination of methanol in man. Previous work on the elimination of methanol has been carried out with animals other than man and has yielded conflicting results. Neymark (1936) and Neymark and Widmark (1936) claimed that the rate of elimination by dogs was independent of the concentration in the body. Haggard and Greenberg (1939), however, concluded that with rats and dogs the rate of elimination was proportional to the concentration of methanol in the body. A similar confusion is found in the literature on the elimination of ethanol (Eggleton, 1940; Haggard and Greenberg, 1934; Carpenter, 1940).

Knowledge of the absorption of methanol by inhalation of the vapour is even more scanty. The reports of Loewy and von der Heide (1914) and Yant and Schrenk (1937) contain a certain amount of information on the rate of accumulation by rats and dogs, but as their experiments were carried out at high vapour concentrations the results are of little value for the present purpose. Further, as the rate of absorption is largely conditioned by the rate of respiration, which varies widely with the size of the animal, one would expect a large difference between man and the lower animals in respect of absorption by inhalation.

Absorption and elimination of methanol were therefore studied with human subjects. Though such an investigation can only be carried out under laboratory conditions, it is desirable to test the conclusions under conditions of industrial practice. We were therefore glad of an opportunity to investigate conditions prevailing in the methanol synthesis plant of Messrs. Imperial Chemical Industries (Fertiliser and Synthetic Products) at Billingham.

The Effect of Ethanol on Methanol Poisoning

While this work was in progress a report by Røe (1943) became available in which case records of 16 patients suffering from methanol poisoning were described. From these cases Røe concluded that the injurious effects of methanol were reduced by the simultaneous ingestion of ethanol. Subsequent and more extensive observations have confirmed this view (Røe, 1946; Dérobert and Hadengue, 1949; Agner, Höök, and von Porat, 1949). It appeared that ethanol might act favourably by inhibiting the conversion of methanol into some more toxic product, e.g. formaldehyde or formate, and it seemed likely that such inhibition would be reflected in an increased output of unchanged methanol. The effect of ingestion of ethanol on the elimination of a standard dose of methanol was therefore studied. Striking effects were observed and it was shown *in vitro* that ethanol exerts a powerful inhibitory effect on the oxidation of methanol by liver alcohol dehydrogenase. A preliminary note of this work has already been published (Zatman, 1946).

Methods

Determination of Methanol.—The method used was that originally proposed by Denigès (1910) as modified by Wright (1927). It involves oxidation by means of acid permanganate to formaldehyde which is then determined colorimetrically with a modified Schiff's

* Throughout this paper the term "elimination" is used to indicate the disappearance of methanol from the body without any assumptions as to the mechanism of its removal. Where specific mechanisms, such as urinary excretion, are considered, these are specified.

reagent. It was found that the sensitizing effect of ethanol on the determination increased with increase in the concentration of ethanol to a maximum between 1·2% and 1·8% ethanol. Solutions under test were therefore always adjusted to contain approximately 1·5% ethanol before analysis. This gave maximal sensitivity and eliminated the possibility of errors due to the presence of small amounts of ethanol in the test samples. In contrast to the experience of Wright it was found that both stages of the estimation were sensitive to temperature variations. The entire process was therefore carried out in a thermostat at 25° C. Optical densities were determined with the Spekker absorptiometer using the yellow-green filter. With these modifications concentrations of methanol up to 15 mg. per 100 ml. could be determined to within 3%.

For the determination of methanol in urine, 10 ml. of the urine were treated with 2 ml. 4/3 NH_2SO_4 and 1 ml. 10% sodium tungstate, and the mixture distilled in an all-glass apparatus (Nicloux, Le Breton, and Dontcheff, 1934). The first 5 ml. of distillate were collected in a graduated flask and analysed for methanol as described above. In 15 control determinations the recovery of added methanol was 96·4 ± 1·2% (standard error). Normal urine from six human subjects gave small blank values, the mean for 20 determinations being 0·3 mg. per 100 ml. expressed as methanol. As the experiments carried out were of a comparative nature, this blank value was unimportant. Tests for the presence of formaldehyde in the urine distillates were consistently negative.

For the determination of methanol in blood, deproteinization was carried out by the usual Folin-Wu method, and 10 or 15 ml. of the filtrate were distilled. As in the case of urine, 5 ml. of distillate were collected and used for the estimation. Recovery of added methanol was 94–96%, and normal blood (cat or human) gave no appreciable blank value.

For the determination of methanol in air, the air was drawn through a train of four drechsel bottles, each containing 150 ml. of water, in series with a gas meter. The contents of the bottles were then mixed and the methanol content determined as above. Recovery of methanol evaporated into the air stream was 96–98% at methanol concentrations of 1–10 mg. per l. and the rate of flow about 2 l. per minute.

Assessment of Methanol Content of the Body.—In a study of this kind with human subjects the toxicity of the methanol precludes the use of large doses. The concentration of methanol in the body water being therefore rather small, the analysis of urine, which is readily available in comparatively large quantities, is a more convenient and practicable index of the concentration of methanol than is analysis of blood. According to Yant and Schrenk (1937), methanol administered to experimental animals becomes uniformly distributed about the tissues of the body according to their relative water content. The same has been demonstrated for ethanol by Nicloux (1934) and Harger, Hulpieu, and Lamb (1937). Further, Haggard, Greenberg, Carroll, and Miller (1940), and Eggleton (1942) have provided evidence that after giving ethanol to man there is a constant relationship between blood concentration and concentration in urine contemporaneously secreted. This is determined by the relative water content of the two fluids, the kidney having no selective action on the distribution of the alcohol between them. Further, to justify the use of urinary methanol concentration as an index of methanol concentration throughout the body water, the constancy of the blood/urine relationship was confirmed using cats as experimental subjects.

The cat was anaesthetized with chloralose (80 mg. per kg.) and the bladder emptied and cannulated, the bladder contents being kept as a control sample. A suitable dose of methanol (100–270 mg. per kg.), diluted with Ringer solution, was then injected into the femoral vein and samples of blood from the carotid artery and of urine were taken at intervals of 30 to 60 minutes for four to five hours. The methanol concentration in each sample was determined as described above. To promote an adequate rate of urine flow it was found expedient to give injections of 5 ml. of 7·5% sodium sulphate via the femoral vein at quarter-hour intervals.

Experiments on Man.—The subjects were five adult males. The dose of methanol which varied from 2·5 to 7·0 ml. (29–84 mg./kg.) was diluted to 100 ml. with water and taken immediately after emptying the bladder before breakfast. Urine was collected after one and two hours, and then every two hours for a period which varied in different experiments from 11 to 16 hours. The total volume at each voiding was noted and the urines were preserved with a small amount of H_2SO_4 and kept at 4° C. until the methanol concentrations had been determined. Pure methanol and clinical absolute ethanol (benzene-free) were used throughout the experiments.

Inhalation Experiments.—The subject was exposed to a known concentration of methanol vapour for two to four hours and the absorption* of methanol was followed by analysis of urine voided at frequent intervals. The exposures were carried out in a small room (22·9 cu.m. capacity) with no windows and two doors separated by an air lock. The doors were felted at the edges to prevent the escape of methanol. The desired concentration of methanol was established in the chamber by rapid evaporation of the calculated quantity of methanol by allowing it to drip from a burette on to a hot plate in the draught of an electric fan. The subject then entered the chamber, and the methanol vapour concentration was maintained at a constant level by continuous evaporation of methanol at a predetermined rate. The air of the chamber was kept in motion by the electric fan, and in each experiment the concentration of methanol was determined at half-hour intervals by the method outlined above. In practice it was found that the methanol concentration in the chamber could easily be kept within 10% of the mean.

* It will be noticed that the "absorption" measured is really the balance of methanol absorbed minus that eliminated during the period of exposure. The term accumulation more accurately describes the overall process, but to avoid confusion this term is reserved for the long term accumulation of methanol after repeated intermittent exposures.

The bladder was emptied immediately before entering the chamber and at intervals of approximately 30 minutes during the experiment. The urine was collected in stoppered bottles and the methanol content determined as described above. To promote the flow of urine, water and coffee were taken before the experiment.

Results

Relation between Concentrations of Methanol in Blood and Urine.—The results of two experiments on cats are shown graphically in Fig. 1. The concentrations of methanol in blood and urine follow a similar course. The constancy of the ratio (concentration in urine : concentration in blood) is seen in Table 1. The mean value of the ratio was 1·29, agreeing well with the figure of 1·3 found by Haggard and others (1940) for ethanol in man. The relationship was further checked by a few determinations of the methanol content of blood in human subjects, during the elimination of methanol. The results are given in Table 2. The values for the ratio (concentration in urine : concentration in blood) are based on single determinations and show more variation than in the experiments with cats, probably due to the difficulty of accurately estimating such low concentrations of methanol in blood. Taken together, however, the results in Tables 1 and 2 suggest that, provided the bladder is emptied fairly frequently, the urinary methanol concentration is a reliable index of the concentration of methanol in the body water during the period of secretion.

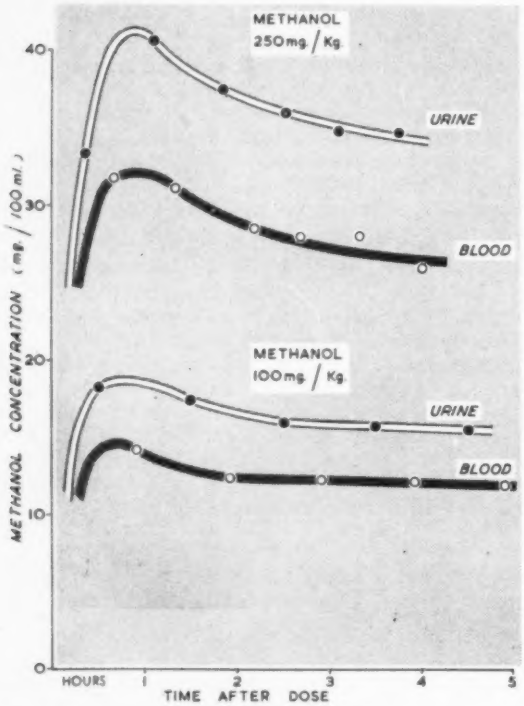


FIG. 1.—The concentration of methanol in blood and urine of the cat after methanol.

TABLE 1

RELATION BETWEEN METHANOL CONCENTRATION IN BLOOD AND URINE IN THE CAT

Cat No.	Dose of Methanol (mg. per kg.)	CB*	CU*	CU/CB
3H	100	12·15	15·7	1·29
4H	250	27·0	35·2	1·30
5H	250	27·5	35·0	1·27
1H	270	31·7	41·2	1·30
			mean	1·29

* Each value for the blood (CB) is the mean of the last four determinations in each experiment, and each value for the urine (CU) the mean of the last three determinations. The concentrations are expressed in mg. per 100 ml. blood or urine.

TABLE 2

RELATION BETWEEN METHANOL CONCENTRATION IN BLOOD AND URINE IN MAN

Subject	Dose of Methanol (mg. per kg.)	Time after Dose (hr.)	CB	CU	CU : CB
H.S.R.	71	2·5	5·33	7·5	1·41
		4·5	4·2	5·4	1·29
L.J.Z.	83·5	2	7·6	9·2	1·21
		4	6·75	8·4	1·24
G.L.	71	3	4·7	6·40	1·36
		5	3·2	4·1	1·28
			Mean		1·30

Each value for blood (CB) represents a single determination, the value for urine (CU) at the same time being obtained from the corresponding elimination curve plotted as in Fig. 2. The concentrations are expressed in mg. per 100 ml. of blood or urine.

Elimination of Methanol.—The variation of urinary methanol concentration with time after the ingestion of three different doses of methanol by the same subject is shown in Fig. 2. These results are typical of a number of experiments carried out with different subjects. Evidence has been presented in the foregoing section of this paper which justifies the assumption that the urinary methanol concentrations may be taken fairly to represent the average methanol concentrations in the body-water during

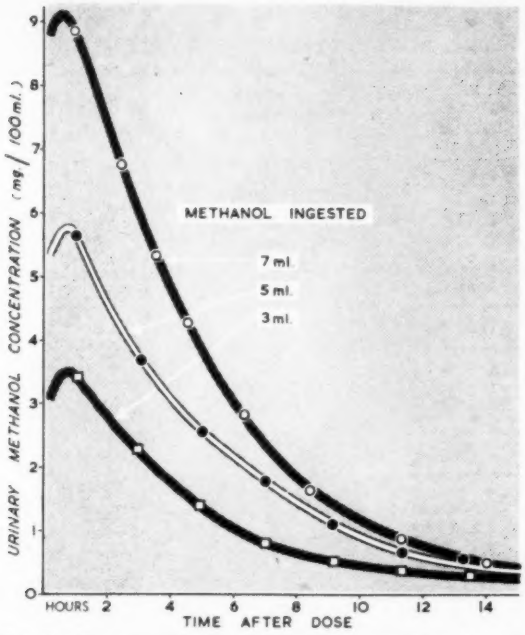


FIG. 2.—The concentration of methanol in human urine after ingestion of methanol. Subject, G.L., weight 78·5 kg.

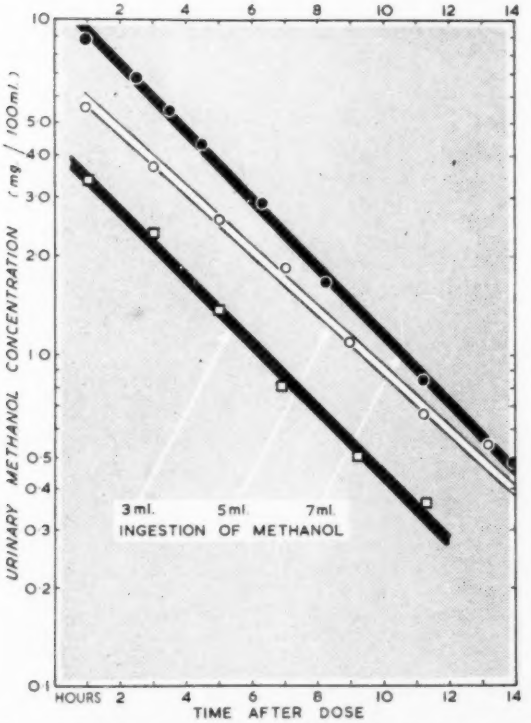


FIG. 3.—The concentration of methanol in urine after ingestion of methanol plotted on a half-log. scale. Data as for Fig. 2.

the period of secretion of each specimen of urine. The curves indicate that the absorption of methanol was rapid, as was to be expected with small doses on an empty stomach. After reaching a maximum within about one hour, the concentration fell rapidly at first, then more slowly, until control values were reached again after 13 to 16 hours. When the logarithms of urinary concentrations are plotted against time, as in Fig. 3, the points conform closely to straight lines. The curves in Fig. 3 may be represented by an expression similar to that derived by Gaddum (1944), i.e.

$$\log C = \log C_o - kt$$

where C_o* and C are the urinary methanol concentrations at zero time and t hours respectively and k a constant for the individual. The values of k for subject G.L. calculated from the data plotted in Fig. 3 were 0·104, 0·099, and 0·094 for the three dosage levels (C and C_o expressed as mg. per 100 ml. urine and t in hours). Values obtained from similar experiments with H.S.R. and L.J.Z. were 0·097, 0·102, 0·106, and 0·108, 0·099, 0·101 respectively. Thus the course of methanol elimination under these conditions was exponential and the rate of elimination at any time was proportional to the methanol concentration in the body at that time.

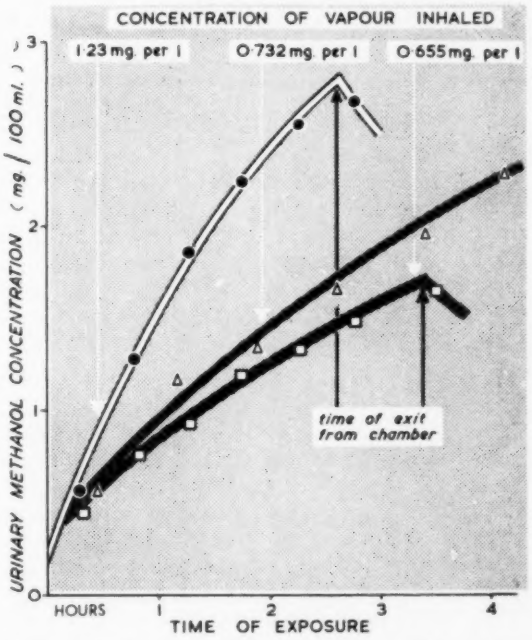

CONCENTRATION OF VAPOUR INHALED
1·23 mg. per l
0·732 mg. per l
0·655 mg. per l
URINARY METHANOL CONCENTRATION (mg./100 ml.)
time of exit from chamber
HOURS 1 2 3 4
TIME OF EXPOSURE

FIG. 4.—Absorption of methanol by inhalation of the vapour. Subject, L.J.Z.

* C_o is the hypothetical value for the concentration of methanol in the urine excreted at zero time if the absorption and distribution of the methanol were instantaneous.

TABLE 3

ABSORPTION OF METHANOL BY INHALATION OF THE VAPOUR

Subject	Concentration of Methanol in Air (mg. per l.)	Urinary Methanol Concentration at 1·6 hr.	Rate of Absorption	Urinary Methanol Concentration at 2·5 hr.	Rate of Absorption
G.L. ..	0·7	0·56	0·50	0·78	0·45
	0·73	0·77	0·63	1·05	0·57
	1·35	1·46	0·63	2·06	0·61
	1·375	1·58	0·70	—	—
	1·43	1·88	0·79	2·56	0·72
	1·43	2·00	0·84	—	—
			Mean 0·68		Mean 0·59
L.J.Z. ..	0·65	0·76	0·7	1·03	0·64
	0·73	0·94	0·77	1·32	0·72
	1·23	1·90	0·92	2·54	0·84
			Mean 0·80		Mean 0·73

Values for the urinary methanol concentration are in mg. per 100 ml., and are corrected for the control value (on entry into chamber). Values for the rate of absorption were obtained by dividing the values in the preceding column by the time and the concentration of methanol inhaled (col. 2).

Only a very small fraction of such doses of methanol appears in the urine ; in different experiments it varied between 0·4 and 1·2% with a mean of 0·7%. A small number of determinations of the methanol content of the expired air indicated that the loss by expiration was of the same order or slightly larger than the loss in the urine.

Absorption of Methanol by Inhalation.—The increase in urinary methanol concentration during the inhalation of various concentrations of methanol vapour are shown for two subjects in Figs. 4 and 5. Values for the urinary methanol concentration at 100 and 150 minutes taken from these curves are given in Table 3. On theoretical grounds one would expect the rate of absorption to decrease exponentially with time (Haggard, 1924 ; Gaddum, 1944). The results do show such a trend but the experiments reported are too few and of too short duration to provide useful information on this point. Under the conditions of the experiments exposures of three to four hours were as long as could reasonably be tolerated.

Values for the rate of absorption given in Table 3 show some variation, due in part to the difficulty of controlling the conditions of such an experiment where the subject is also the operator. For the purpose of these experiments, however, it may be taken that under these conditions the rate of absorption for each subject is approximately proportional to the concentration of vapour inhaled.

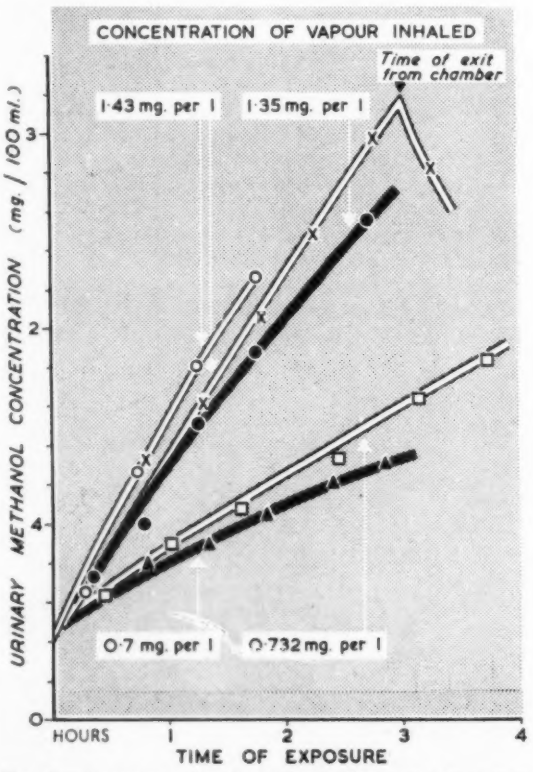


FIG. 5.—Absorption of methanol by inhalation of the vapour. Subject, G.L.

Effect of Ethanol on Elimination of Methanol.—Ingestion of ethanol during the elimination of methanol had a striking effect on the elimination curves. Figs. 6 to 8 show the results of experiments in which ethanol was taken at various times during the elimination of a fixed dose (4·0 ml.) of methanol.

Other data relevant to these experiments are given in Table 4.

A single dose of 15 ml. of ethanol, taken simultaneously with the methanol, caused a marked elevation in the peak concentration of methanol attained (Fig. 6). The time required for the methanol concentration to return to control levels was not obviously affected by such a dose of ethanol. The increase in the peak concentration is attributable to an inhibition by the ethanol of the main process of methanol elimination, i.e. oxidation. The ethanol, however, only operates in this way during the first hour or so of the experiment, since within this time such a dose of ethanol is itself completely eliminated from the body (Eggleton, 1942), so that the total methanol elimination time is not appreciably prolonged. The good reproducibility of the elimination curves in the same subject on different occasions is also illustrated in Fig. 6.

The transient effect of a single dose of ethanol is more clearly seen in Fig. 7. In one experiment the ethanol was taken five hours after the methanol. It effectively arrested the decline in body methanol concentration, which returned to its original rate after about two hours. In another

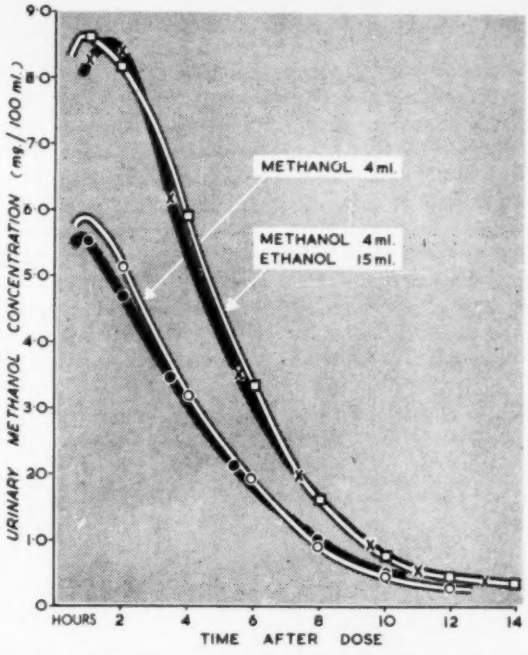


FIG. 6.—The concentration of methanol in urine after ingestion of methanol and of methanol and ethanol simultaneously. Subject L.P.K., weight 63·1 kg.

TABLE 4

EFFECT OF ETHANOL ON EXCRETION OF METHANOL IN URINE IN THREE HUMAN SUBJECTS

Subject and Body Weight	A.H.G. 67·0 kg.				L.P.K. 63·1 kg.					L.J.Z. 57·0 kg.			
Date	1.7.46	3.6.46	5.7.46	10.7.46	3.6.46	10.6.46	5.6.46	12.6.46	19.6.46	24.6.46	26.6.46	23.6.46	2.7.46
Duration of experiment (hr.)	12	12	10¼	12	12	12	14	13	12	11¼	12	12½	12
Dose (ml.) Methanol (at zero time)	4	4	4	4	4	4	4	4	4	4	4	4	4
Dose (ml.) Ethanol ..	None	15 at 0 hr.	15 at 5 hr.	15 at 0 hr. and 10 each hr. up to 7 hr.	None	None	15 at 0 hr.	15 at 0 hr.	15 at 0 hr. and 10 each hr. up to 7 hr.	None	15 at 0 hr.	15 at 5 hr.	15 at 4½ hr. and 7·5 at 5, 5½, 6, and 6½ hr.
Peak methanol concentration in urine (mg./100 ml.)	6·05	7·95	7·21	8·82	5·50	5·12	8·60	8·35	9·20	7·27	9·75	7·70	7·20
Total volume urine excreted (ml.)	901	1192	726	1364	886	885	1096	857	1722	496	1279	479	1033
Total methanol excreted (mg.)	30·8	56·5	30·9	107·1	21·7	18·2	43·2	38·5	125·5	21·6	87·4	15·3	45·9
% of dose of methanol excreted	0·97	1·78	0·98	3·70	0·68	0·57	1·36	1·21	3·96	0·68	2·75	0·48	1·45

experiment (Fig. 7) a dose of 15 ml. ethanol at four and a half hours was followed by four further doses, each of 7·5 ml., at half-hour intervals. The flattening of the curve during this period indicates the arrest of methanol elimination while an adequate concentration of ethanol was maintained in the body. Fig. 8 shows the results obtained in two subjects when a dose of 15 ml. ethanol taken with the methanol was followed by hourly doses of 10 ml. ethanol for seven hours. Throughout this time the body methanol concentration was maintained at a high level compared

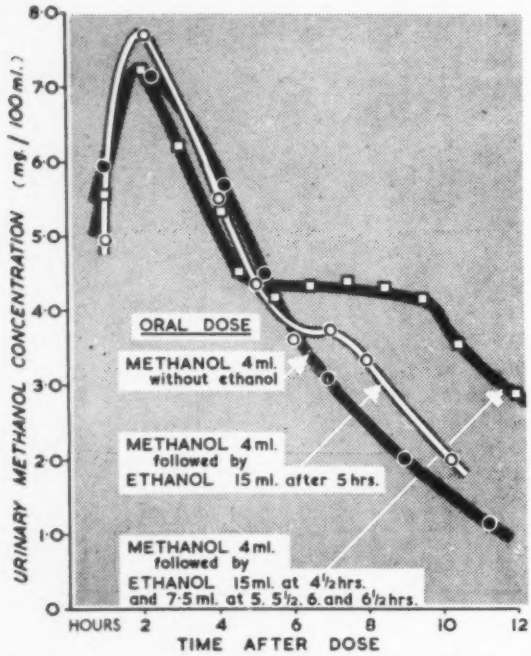

URINARY METHANOL CONCENTRATION (mg. / 100 ml.)
ORAL DOSE
METHANOL 4 ml. without ethanol
METHANOL 4 ml. followed by ETHANOL 15 ml. after 5 hrs.
METHANOL 4 ml. followed by ETHANOL 15 ml. at 4½ hrs. and 7·5 ml. at 5, 5½, 6, and 6½ hrs.
HOURS
TIME AFTER DOSE

FIG. 7.—The concentration of methanol in the urine after an oral dose of (*a*) methanol without ethanol (*b*) followed by ethanol, and (*c*) followed by two doses of ethanol at specific intervals. Subject L.J.Z., weight 57·0 kg.

with controls without ethanol. It declined slowly, at a rate which might be entirely accounted for by loss of methanol in the urine and expired air. About two hours after the cessation of ethanol administration, when the body ethanol might be expected to be approaching zero again, the decline in methanol concentration accelerated to control levels, indicating the release from inhibition of the chief mechanism of elimination. It is of interest to attempt a quantitative estimate of the effect of ethanol on the rate of elimination of methanol in these experiments. This has been done in Table 5. The data used were taken from the curves of Fig. 8, and refer to a time four hours after the ingestion of methanol, when one may safely assume

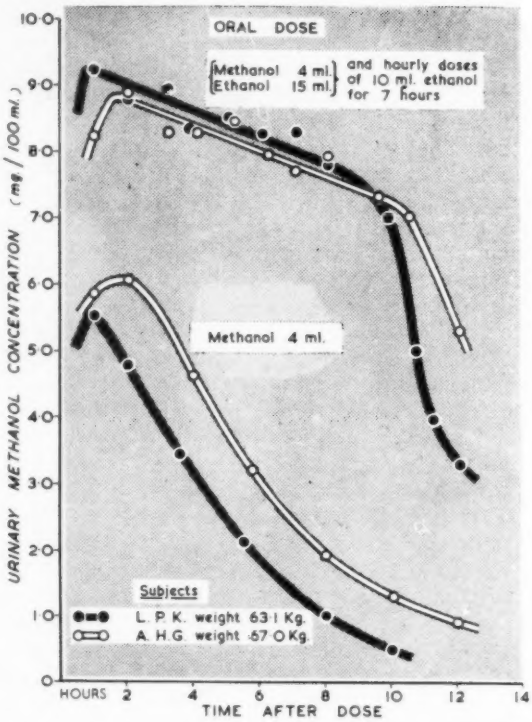

ORAL DOSE
Methanol 4 ml. Ethanol 15 ml. and hourly doses of 10 ml. ethanol for 7 hours
URINARY METHANOL CONCENTRATION (mg. / 100 ml.)
Methanol 4 ml.
Subjects
L. P. K. weight 63·1 Kg.
A. H. G. weight 67·0 Kg.
HOURS
TIME AFTER DOSE

FIG. 8.—The concentration of methanol in the urine after an oral dose of methanol (*a*) without ethanol, and (*b*) with specific doses of ethanol simultaneously and hourly for seven hours.

that absorption of methanol from the alimentary tract is no longer a significant factor in determining the course of the curves. A tangent has been drawn to each curve at the four-hour point, and the slopes of these are given in Table 5 as representing rates of elimination of methanol. Each, however, is associated with a different body methanol concentration, also given in the table. Evidence has already been provided that in this concentration

TABLE 5

EFFECT OF ETHANOL ON RATE OF METHANOL ELIMINATION* BY MAN

Subject	Dose†	Methanol Concentration		Rate of Fall per unit of Magnitude
		Magnitude (mg./100 ml.)	Rate of Fall (mg./100 ml./hr.)	
L.P.K.	(a)	3·0	0·69	0·23
	(b)	8·6	0·21	0·024
A.H.G.	(a)	4·6	0·77	0·15
	(b)	8·35	0·18	0·022

* Data taken from curves of Fig. 8, the figures referring to a time four hours after the ingestion of the methanol.

† (*a*) = 4 ml. methanol; (*b*) 4 ml. methanol + 15 ml. ethanol, and 10 ml. ethanol each hour afterwards.

range the rate of elimination of methanol is proportional to the concentration of methanol in the body. For purposes of comparison, therefore, each rate of elimination has been divided by the corresponding methanol concentration, giving a rate of elimination in mg. per 100 ml. per hr. per unit methanol concentration. The reduction of this rate by the giving of ethanol was by 90% in the case of one subject, by 85% in the other. This is a rough approximation and it is doubtful if significance should be attached to the difference between the two subjects. It is of interest, however, to note that the figures in Table 5 for rate of elimination per unit methanol concentration show a close correspondence for the two subjects when ethanol was present, whereas in the absence of ethanol L.P.K. appears to have eliminated methanol appreciably more rapidly than A.H.G. Significant individual differences seem less likely in the former case, if only physical processes of elimination dependent on escape in urine and expired air are then operating, than in the latter case when the major process is an enzymic oxidation.

Observations in a Factory

The methanol synthesis plant formed an offshoot of the ammonia synthesis plant and the actual " methanol converters " in which methanol is synthesized were housed in the same building as the ammonia converters. The converters were used for synthesizing higher alcohols (ethyl, propyl, butyl, etc.), as well as methanol, and conditions could be varied to produce predominantly methanol or a mixture of methanol and higher alcohols. The product of the latter process was separated into higher alcohols and methanol in a distillation plant referred to as the " stripping plant ". The methanol from this distillation and from the other process was refined in the " methanol distillation plant ". The atmosphere was sampled in all three places mentioned, and urine samples were taken from workers in the methanol distillation and stripping plants. A brief description of conditions of testing in each case is given below.

The air was analysed as described under " Methods ". The air-inlet of the sampling train was placed in positions most likely to give a concentration of methanol vapour in a place habitually frequented by the operatives. Fairly long sampling periods (two to six hours) were used so as to yield a measure of the average concentration at the position chosen. The results are shown in Table 6.

Synthesis Plant.—In this case the air inlet was suspended at a height of about 7 ft. from the wire-mesh working platform at a point situated between the sampling tray (which was equipped with tap-lines from the plant, by means of which samples were taken approximately hourly) and the control panel where the operatives spent most of their time. The air was tested during the day and once during the night shift. As the building was very spacious and the plant a high pressure one, i.e. working at a high pressure, therefore completely closed in, the negative results appended are not surprising.

Methanol Distillation Plant.—In this case the "still " and storage tanks were in the open air, whilst the control panel which the operatives attended was housed in a small building. The " sampling tray " was housed in a small passage along the back of this building, and although the operatives generally entered this part only once an hour to take samples, the air-inlet was placed close to the sampling tray as this was the most likely place to find an accumulation of methanol vapour. In this instance urine samples were taken at the beginning and end of shifts from six workers over

TABLE 6

RESULTS OF AIR ANALYSIS AT I.C.I. METHANOL SYNTHESIS PLANT

Site	Duration of Sampling	Volume of Air Entrained (C)	Methanol Concentration (p.p.m.)
(1) Synthesis plant	11.40 a.m.– 2.25 p.m.	277	<5
	2.35 p.m.– 4.30 p.m.	254	,,
	11.25 p.m.– 2.30 a.m.	175·5	,,
	10.30 a.m.– 4.35 p.m.	378	,,
(2) Methanol distillation plant..	11.02 a.m.– 1.43 p.m.	357	40·5
	1.58 p.m.– 5.05 p.m.	248	64·0
(3) Stripping plant	10.30 a.m.–12.05 p.m.	133·3	82
	12.17 p.m.– 1.46 p.m.	136·5	116
	1.53 p.m.– 4.08 p.m.	156	80

three days. The analysis of all samples gave negative results except for two end-of-shift samples from one worker. The concentration found in these two cases were so small, however, as to be almost negligible.

Stripping Plant.—This plant smelt worst of the three, though the smell was due to uncharacterized " volatile oils " separated in the distillation process. The housing containing the sampling trays, and control panels was built round the columns of the still some height above ground level. The air inlet was suspended in this case close to the control panels, one sample being taken at a remote sampling tray and the other two being taken from the space between two other sampling trays where the operatives had table and chairs and spent most of their time. Samples were taken hourly. Urine samples were taken at beginning and end of shifts from three workers for three days and the results of analysis were again negative.

Discussion

Assessment on Safety Limits for Exposure to Methanol Vapour.—The initial aim of these experiments was to find the threshold for methanol accumulation by finding (1) how much methanol a man could eliminate within 16 hours, and (2) the concentration of methanol vapour which must be inhaled for eight hours to cause the retention of such an amount in the body.

The experiments on the elimination of orally administered methanol showed that after the lapse of sufficient time for complete absorption, the rate of elimination was proportional to the concentration of methanol in the body water. The mechanism of elimination is discussed below, but for the present purpose the finding that elimination follows the equation

$$\log C = \log C_o - kt$$

allows us to calculate the urinary methanol concentration (C_o) corresponding to an amount of methanol which may be disposed of within 16 hours. If elimination is considered to be complete when $C = 0{\cdot}5$ mg. per 100 ml. (average blank value for these experiments), substitution of the observed magnitudes for k in the above equation gives values for C_o of 19·1, 21·5, and 21·6 mg. per 100 ml. for subjects G.L., H.S.R., and L.J.Z. respectively. As the urinary methanol concentration has been shown to be a satisfactory index of the concentration of methanol in the body, these values can be used directly without further manipulation. The degree of exposure giving rise to such urinary methanol concentrations may be estimated using the results of the inhalation experiments. The rates of absorption of methanol observed in experiments are much lower than those observed with smaller animals. Loewy and von der Heide (1914) found a methanol content of 45 mg. per 100 g. in the bodies of rats exposed to a vapour concentration of 2,000 p.p.m. for two hours. The inhalation of methanol vapour at half this concentration (1·35 mg. per l., 1015 p.p.m.) by G.L. gave rise to a urinary methanol concentration of 2·4 mg. per 100 ml. corresponding to an even smaller concentration in the body as a whole. Yant and Schrenck (1937) found blood methanol concentrations of 84 to 100 mg. per 100 g. in dogs exposed to a methanol concentration of 4,000 p.p.m. for 12 hours which suggests an average rate of absorption at least three times as great as the rates observed here. These discrepancies emphasize the necessity for carrying out such experiments on man rather than on the usual experimental animals.

The values for the rate of absorption of methanol given in Table 3 may be used to estimate the methanol vapour concentration, by exposure to which for eight hours the two subjects would attain the critical body methanol content represented by the C_0 values calculated above. For G.L. the rate of absorption was found to be 0·59 ; the critical vapour concentration for this subject would therefore be

$$19{\cdot}1/8 \times 0{\cdot}59 = 4{\cdot}04 \text{ mg. per l. or } 3{,}050 \text{ p.p.m.}$$

The corresponding calculation for L.J.Z. gives 3·70 mg. per l. or 2,780 p.p.m.. For these two subjects, therefore, a concentration of approximately 3,000 p.p.m. of methanol would involve a danger of gradual accumulation of methanol in the body.

The accuracy of these estimates is limited chiefly by the accuracy of the determined rates of absorption which are based on rather few experiments. Extrapolation of the results of these experiments to cover a period of eight hours may involve some error, but in so far as the rate of absorption may be expected to fall as the duration of exposure increased, the critical vapour concentration would be underestimated rather than overestimated. On the other hand, in using these data to judge conditions in industry, it must be remembered that during the inhalation experiments the subjects were in a comparatively resting state. Vigorous activity by stimulating respiration would probably increase the rate of absorption and increase the hazard. Further, as industrial conditions are more difficult to control than those in the laboratory, the permissible maximum concentration should be set at a much lower level, say 10% of the above, i.e. 300 p.p.m. Below this level accumulation is very unlikely to occur, and so far no untoward symptoms have been observed with doses liable to be absorbed

at this level. On this basis safety limits which have previously been proposed, e.g. 100 p.p.m. by the International Labour Office and 200 p.p.m. by von Oettingen (1943), leave a good safety margin.

In the light of these considerations the conditions prevailing in the factory which was investigated were quite adequately controlled and ensured freedom from potential harm for the operators. In positions where the highest vapour concentrations may be expected the average vapour concentration exceeded 100 p.p.m. in only one test. As the men only spent a proportion of the shift in these immediate areas, the presence of no more than traces of methanol in their urine is understandable. This, in turn, confirms that the value suggested above for the maximum permissible concentration of methanol vapour leaves an adequate safety margin. It must be pointed out, however, that the factory investigated was designed with an awareness of the hazard of methanol poisoning, and these observations do not preclude the possibility of danger arising on less well-controlled premises.

Effect of Ethanol on Elimination of Methanol.—Previous work on the elimination of methanol has been carried out on animals other than man and has yielded conflicting results. Neymark (1936) and Neymark and Widmark (1936) claimed that the rate of elimination from dogs was independent of the dose level. Haggard and Greenberg (1939), on the other hand, concluded that in rats and dogs the rate of elimination was proportional to the concentration of methanol in the body. According to the latter workers the greater part of the ingested methanol was excreted in the expired air as a result of simple diffusion, and the rate of excretion was therefore directly proportional to the concentration in the blood. Using rats, they recovered from the expired air 70% of the methanol which had disappeared from the body, in an experimental period during which, however, only 6% of the whole dose was eliminated. Asser (1914) and Völtz and Dietrich (1912) found, respectively, 53% and 30% of the dose excreted in the expired air of dogs.

In the present work the experiments on man showed that, after the lapse of sufficient time to ensure complete absorption, the rate of elimination of methanol was proportional to its concentration in the body water, and in this respect the findings of Haggard and Greenberg were confirmed, but excretion via the lungs does not appear to have played a major part. Rough calculations using Haggard and Greenberg's formula suggest that the elimination of such doses of methanol via the expired air alone would have taken several days whereas in fact 12 to 16 hours were found sufficient. As the urinary loss represented on the average less than 1% of the dose taken, and respiratory loss little more, it is clear that metabolic processes must have been chiefly responsible for the disappearance of methanol from the body. By appropriate administration of ethanol, it was found possible to reduce the rate of methanol elimination by about 90%. This striking effect cannot be attributed to any action of ethanol on the purely physical processes of elimination of methanol via lungs or kidney, and it therefore identifies the main methanol eliminating process under the conditions of our experiments and in the absence of ethanol as a metabolic process. Further support for this view can be found in the data recorded in Table 4. The fraction of the methanol which appears in the urine is actually increased by the presence of ethanol. A single simultaneous dose of ethanol increased the fraction excreted from 0·7% to 1·8% and repeated ingestion of ethanol raised it to almost 4%. (These values are averages of the results from the appropriate experiments in Table 4.)

The disagreement with Haggard and Greenberg as regards the relative importance of respiratory elimination may readily be resolved when the difference in dosage is taken into consideration. Haggard and Greenberg gave doses of 1 to 4 g. per kg., far greater than can be used in experiments on man. In the present work doses of from 0·029 to 0·084 g. per kg. were used. It is most probable that at low body methanol concentrations the alcohol is removed chiefly by an enzymic reaction. With increasing concentration, a limit to the rate of removal by this route is reached when the enzyme becomes saturated with its substrate. Urinary and respiratory elimination are never restricted by such a limit and at a sufficiently high methanol concentration must be expected to play a dominant part. The exponential nature of the methanol elimination curves in our experiments suggests that the prevalent methanol concentration was well below that required to saturate the enzyme, falling in the region where reaction is roughly proportional to substrate concentration.

There is no reason to doubt that the enzymic removal of methanol is achieved by a process of oxidation. Lutwak-Mann (1938) demonstrated the ability of horse liver alcohol dehydrogenase to oxidize methanol, as well as ethanol, to the corresponding aldehyde, but found the rate of reaction to be much slower in the former case. The conversion of methanol to formaldehyde by alcohol dehydrogenase *in vitro* has been confirmed, and ethanol has been shown to exert a powerful competitive inhibitory effect on this oxidation. Inhibition was almost complete when the molar ratio of

ethanol to methanol was as little as 1 to 15. This appears to justify the suggestion that the *in vivo* effects of ethanol on methanol elimination were due to an inhibition of the oxidation of methanol by alcohol dehydrogenase. Eggleton's observations (1942) indicate that the peak blood ethanol concentration in man after a dose of 15 ml. is about 30 mg. per 100 ml., and that about 10 ml. of ethanol are metabolized per hour at such concentration levels. The method of recurrent ethanol administration adopted in our experiments might be expected therefore to maintain a body ethanol concentration high enough to suppress methanol oxidation.

In a later review of 83 cases of methanol poisoning Røe (1946) felt confirmed in his earlier (1943) impression that the toxic symptoms of methanol poisoning, particularly the amblyopia, tended to be minimized by the concurrent drinking of ethanol (see also Dérobert and Hadengue, 1949). There is a widespread belief that these toxic effects are not caused by methanol itself, but by a metabolic product, probably formaldehyde and/or formate (Keeser, 1931 ; Keeser and Alberty, 1948 ; Flury and Wirth, 1936 ; Fink, 1943 ; Røe, 1943, 1946). Evidence in support of this view has been obtained by experiments with surviving retina (to be reported elsewhere). It was found that methanol had no effect on the metabolism of ox retina even at a concentration of M 20. Of the metabolic products of methanol, formate had a weak inhibitory effect on retinal respiration and formaldehyde strongly inhibited both aerobic respiration and anaerobic glycolysis.

Asser (1914) had previously found that simultaneous administration of ethanol, amyl alcohol, or acetone reduced the urinary excretion of formate by dogs after the ingestion of methanol, an effect recently confirmed by Bastrup (1947) in dogs and rabbits, but he concluded that these substances did so by increasing the permeability of cell membranes to formate thus facilitating further oxidation of this product. Røe suggests an alternative explanation, that the diminished excretion of formate was caused by a reduction in the rate of formation due to the capacity of ethanol " to displace methanol from the surface of cells, its oxidation to formic acid being thereby checked ". More recently Agner and Belfrage (1947) observed a decreased rate of fall of the blood methanol concentration after the simultaneous injection of ethanol in rabbits. This observation and our own results provide a more rational basis for explaining a favourable effect of ethanol as the result of an inhibition of methanol oxidation, and might justify attempts to use ethanol therapeutically in methanol poisoning in an endeavour to maintain the inhibition long enough to secure elimination of the methanol unchanged by the respiratory and urinary routes. Such a use of ethanol has indeed recently been reported by Agner, Höök, and von Porat (1949). Only two patients were treated, however, and of these, one recovered and one died.

It is perhaps significant that only two or three cases of blindness have been reported from the drinking of methylated spirits in this country, although the drinking of this spirit is apparently quite widespread. The above results suggest that the large proportion of ethanol in the spirit (about 95%) would indeed reduce very markedly the toxic effects of the methanol.

Summary

Owing to the slow rate of elimination of methanol from the body, repeated exposure to the vapour or liquid may result in accumulation and under such conditions the use of methanol would constitute a toxic hazard. The present work was carried out in order to determine the maximum concentration of methanol vapour, exposure to which for eight hours is consistent with complete elimination of absorbed methanol during the subsequent 16 hours. The absorption and elimination of methanol were therefore studied in man.

The concentration of methanol in the body was followed by determination of the concentration in the urine. The reliability of this procedure was confirmed by experiments with the cat and with human subjects.

The elimination of methanol after doses of 2·5 to 7·0 ml. has been studied in five human subjects. At any time the rate of elimination was found to be proportional to the concentration of methanol in the body. The significance of this finding is discussed. Only a very small fraction of the ingested methanol (about 2%) was eliminated via the respiratory and urinary routes.

The rates of absorption of methanol by two human subjects during exposure to vapour concentrations of 0·6 to 1·5 mg. methanol per l. (400–1,000 p.p.m.) have been investigated. Over short periods the amount of methanol absorbed appears to be approximately proportional to the duration of exposure and to the concentration of vapour in the atmosphere.

By examination of the results of the absorption and elimination experiments it was concluded that exposure to a methanol vapour concentration of about 3,000 p.p.m. for eight hours a day may cause accumulation of methanol in the body and thus give rise to a toxic hazard. It is suggested that the maximum concentration of methanol

vapour to which workers may be safely exposed is 300 p.p.m.

Observations made at the methanol synthesizing plant of I.C.I. Ltd. are described. Estimation of the methanol concentrations in the air and in the urine of the operatives showed that conditions were satisfactorily controlled.

The ingestion of ethanol, together with or shortly after methanol, reduced the rate of elimination of the latter by up to 90%. Evidence is adduced to show that this is due to inhibition of the metabolic oxidation of methanol.

These results provide a rational basis for explaining the favourable effect of ethanol on the course of methanol poisoning such as Røe reports, and might justify attempts to use ethanol therapeutically.

We should like to express our sincere thanks to the late Professor H. S. Raper, C.B.E. and Dr. L. P. Kendal for their constant interest in this work and their assistance as experimental subjects; to Professor A. A. Harper, for assistance with the cat experiments, and to Dr. A. H. Gowenlock for being an experimental subject. Our thanks are also due to Dr. Schilling and Messrs. I.C.I. Limited for arranging the investigations at Billingham.

The cost of this work was partly defrayed by the Medical Research Council, to which we are also grateful for a grant to one of us (L.J.Z.).

REFERENCES

Agner, K., and Belfrage, K. E. (1947). *Acta. physiol. scand.*, **13**, 87.
——, Höök, O., and von Porat, B. (1949). *Quart. J. Stud. Alcohol*, **9**, 515.
Asser, E. (1914). *Z. exp. Path. Ther.*, **15**, 322.
Bastrup, J. T. (1947). *Acta pharmacol.*, **3**, 312.
Browning, E. (1937). Med. Res. Coun. Industrial Health Research Board. Rep. no. 80.
Carpenter, T. M. (1940). *Quart. J. Stud. Alcohol*, **1**, 201.
Chew, W. B., Berger, E. H., Brines, O. A., and Capron, M. J. (1946). *J. Amer. med. Ass.*, **130**, 61.
Denigès, G. (1910). *C.R. Acad. Sci., Paris*, **150**, 529, 832.
Dérobert, L., and Hadengue, A. (1949). *Chem. Abstr.*, **43**, 3105.
Egg, C. (1927). *Schweiz. med. Wschr.*, **8**, 5.
Eggleton, M. G. (1940). *J. Physiol., Lond.*, **98**, 228, 239.
——(1942). *Ibid.*, **101**, 172.
Fink, W. H. (1943). *Amer. J. Ophthal.* **26**, 694.
Flury, F., and Wirth, W. (1936). *Arch. Gewerbepath. Gewerbehyg.*, **7**, 221.
Gaddum, J. H. (1944). *Nature, Lond.*, **153**, 494.
Haggard, H. W. (1924). *J. biol. Chem.*, **59**, 753.
——, and Greenberg, L. A. (1934). *J. Pharmacol.*, **52**, 150, 167.
——, ——, (1939). *Ibid.*, **66**, 479.
——, ——, Carroll, R. P., and Miller, D. P. (1940). *J. Amer. med. Ass.*, **115**, 1680.
Hamilton, A. (1925). "Industrial Poisons in the United States." New York.
Harger, R. N., Hulpieu, H. R., and Lamb, E. B. (1937). *J. biol. Chem.*, **120**, 689.
Humperdinck, K. (1941). *Arch. Gewerbepath. Gewerbehyg.*, **10**, 569.
Jacobson, B. M., Russell, H. K., Grimm, J. J., and Fox, E. C. (1945). *Nav. med. Bull., Wash.*, **44**, 1099.
Kaplan, A., and Levreault, G. V. (1945). *Ibid.*, **44**, 1107.
Keeser, E. (1931). *Arch. exp. Path. Pharmak.*, **160**, 687.
——, and Alberty, J. (1948). *Klin. Wschr.*, **26**, 212.
Loewy, A., and von der Heide, R. (1914). *Biochem. Z.*, **65**, 230.
Lutwak-Mann, C. (1938). *Biochem. J.*, **32**, 1364.
McCord, C. P. (1931). *Industr. Engng. Chem.*, **23**, 931.
McGregor, I. S. (1943). *Brit. J. Ophthal.*, **27**, 523.
Macht, D. I. (1920). *J. Pharmacol.*, **16**, 1.
Munch, J. C., and Schwartze, E. W. (1925). *J. Lab. clin. Med.*, **10**, 985.
Neymark, M. (1936). *Skand. Arch. Physiol.*, **73**, 227.
——, and Widmark, E. M. P. (1936). *Ibid.*, **73**, 283.
Nicloux, M. (1934). *Bull. Soc. Chim. biol., Paris*, **16**, 330.
——, Le Breton, E., and Dontcheff, A. (1934). *Ibid.*, **16**, 1314.
——, and Placet, A. (1912). *J. Physiol. Path. gén.*, **14**, 916.
Oettingen, W. F. von (1943). "The Aliphatic Alcohols." U.S. Pub. Health Service, Pub. Health Bull. No. 281. Govt. Ptg. Office, Washington.
Poulsson, E. (1941). "Lehrbuch der Pharmakologie," 12th ed. Leipzig and Oslo.
Richardson, B. W. (1869). *Med. Times, Lond.*, **2**, 703.
Røe, O. (1943). *Acta. med. scand.*, **113**, 558.
——(1946). *Ibid.*, **126**, Suppl. 182.
Rost, E., and Braun, A. (1926). *Arb. ReichsgesundhAmt.*, **57**, 580.
Sayers, R. R., Yant, W. P., Schrenk, H. H., Chornyak, J., Pearce, S. J., Patty, F. A., and Linn, J. G. (1944). *J. industr. Hyg.*, **26**, 255.
Scott, E., Helz, M. K., and McCord, C. P. (1933). *Amer. J. clin. Path.*, **3**, 311.
Tyson, H. H., and Schoenberg, M. J. (1914). *J' Amer. med. Ass.*, **63**, 915.
Uhthoff, W. (1915). *Klin. Mbl. Augenheilk.*, **54**, (1), 48.
Völtz, W., and Dietrich, W. (1912). *Biochem. Z.*, **40**, 15.
Weese, H. (1928). *Arch. exp. Path. Pharmak.*, **135**, 118.
Widmark, E. M. P. (1933). *Biochem. Z.*, **259**, 285.
Witte, R. (1933). *Arch. Gewerbepath. Gewerbehyg.*, **5**, 58.
Wright, L. O. (1927). *Industr. Engng. Chem.*, **19**, 750.
Yant, W. P., and Schrenk, H. H. (1937). *J. industr. Hyg.*, **19**, 337.
——, ——, and Sayers, R. R. (1931). *Industr. Engng. Chem.*, **23**, 551.
Zatman, L. J. (1946). *Biochem. J. Proc.*, **40**, lxvii.
Ziegler, S. L. (1921). *J. Amer. med. Ass.*, **77**, 1160.

Brit. J. industr. Med., 1952, **9**, 32.

THE DETERMINATION OF SMALL AMOUNTS OF TETRANITROMETHANE IN AIR

BY

V. B. VOUK and O. A. WEBER

From the Institute of Industrial Hygiene, Zagreb, Yugoslavia

(RECEIVED FOR PUBLICATION OCTOBER 17, 1951)

Tetranitromethane (T.N.M.) occurs in the production of T.N.T. as a byproduct of toluene nitration. It is a highly toxic substance, and its toxic properties have been recently investigated by Sievers, Rushing, Gay, and Monaco (1947). According to them, the maximum allowable concentration of T.N.M. is less than 5 p.p.m. Elkins (1950) recommends 0·5 p.p.m. or 4 mg./m.^{3} of air as the safe maximum allowable concentration. Unless we are prepared to take very large air samples, the analytical method for determining T.N.M. should enable us to determine with precision as little as 20 μg., that is, the amount of T.N.M. in a 5 litre air sample, if the concentration of the contaminant equals the maximum allowable concentration. As the volume of absorption liquid usually does not exceed 10 ml., a reliable analytical method should register with sufficient precision a concentration of 2 μg. of T.N.M. per millilitre of the solution.

Baillie, Macbeth, and Maxwell (1920) describe a method for determining T.N.M. based on the reduction of T.N.M. by hydrazine. The nitrogen evolved during the reduction is determined volumetrically. However, this method does not seem sensitive enough for industrial practice, since only 0·2 ml. of nitrogen is produced per 35 mg. of T.N.M. A colour reaction between dioxane and T.N.M. is described by Reid and Hoffmann (1929). This reaction is used to indicate the presence of dioxane, and we tried to invert and adapt it for the determination of T.N.M., but without success, its sensitivity being insufficient. The method of Kranz and Štepanek (1937), based on the fact that iodine is liberated when potassium iodide is added to a solution of T.N.M., can be used only for determining larger quantities of T.N.M. (0·05–0·12%). Ehrenberg, Fisher, and Löfgren (1945) determined small quantities of T.N.M. by means of the Griess-Ilosvay reaction, which, however, is not specific for T.N.M., and other contaminants such as nitrous gases would interfere if present. The polarographic method of Cruse and Haul (1949) would be satisfactory with regard to sensitivity (9·8 to 98 μg./ml.), but if m-dinitrobenzene or s-trinitrobenzene are present, a preliminary separation of T.N.M. by vacuum distillation becomes necessary. Thus only the method of Sievers and others seemed to satisfy the requirements both with regard to sensitivity and simplicity. However, there remained several points to be cleared up before the method of Sievers and his colleagues could be accepted with complete confidence. The method is based on a colour reaction between T.N.M. and benzidine in ethanol. One of the problems studied in this paper is the stability of the colour produced by mixing alcoholic solutions of T.N.M. and benzidine. Sievers states that " the colour is sufficiently stable, but not stable enough to permit the use of the same set of standards for comparison with samples made up at other times ". When preparing the calibration curve according to the procedure of Sievers and others we noticed that the optical density of a sample made twice in the same way could not be reproduced. This induced us to study in the first place the influence of light on the intensity of the colour reaction. Other problems we studied were the optimum amount of benzidine, the influence of the design of the apparatus for measuring the optical density, the influence of ageing of the T.N.M. solution on the intensity of the colour reaction, the influence of various other contaminants such as nitrobenzene, HNO_3, and finally the efficiency of the sampling procedure.

Experimental

Chemicals.—The following were used :—

Tetranitromethane synthetized according to Poe Liang (1941) $n_D^{16·4} = 1·44145$.

Ethanol, commercial, 96%, redistilled.

Pyridine, pure (Schering-Kahlbaum, Berlin).

Benzidine, purest (Schering-Kahlbaum, Berlin).

Density Measurements.—Density* measurements were performed with a Beckman spectrophotometer, model DU, a Fisher electrophotometer, A.C. model, and a Pulfrich photometer (C. Zeiss, Jena). All measurements with the Beckman spectrophotometer were carried out at $\lambda = 400$ mμ with a slit of 0·06 mm. Light filters B with maximum transmission at 425 mμ and K—8a—VI (blue) were used with the Fisher and Pulfrich photometers respectively. The optical path length was 1·002 for the Beckman and 0·999 for the Pulfrich photometer. Cylindrical cells, of 1·2 cm. diameter, were used in the Fisher electrophotometer.

Mixtures of T.N.M. and air of known concentration were prepared with an apparatus similar to that described by Scott (1943). The colour reaction was performed by adding a measured amount of benzidine solution in ethanol (1·00 g./litre) to the T.N.M. solution in ethanol, the *p*H of which was brought to 6 by means of pyridine.

Influence of Light on Intensity of Colour Reaction

The influence of light on the intensity of colour reaction is shown in the Fig. 1.

The reaction was carried out in daylight. The absorption cell was filled with the reaction mixture and put immediately into the compartment of the Beckman spectrophotometer. A combination of the ordinary cell compartment and the fluorescence accessory set enabled us to illuminate the reaction mixture and to measure the density at the same time. When the cell was not illuminated, the optical density of the reaction mixture increased first very rapidly, then more slowly, reaching finally a maximum value. As soon as the light was put on, the optical density fell. After 15 to 20 minutes the density stabilized itself again at a value 25% lower than the maximum density. When the light is put off again, the density increases but not so rapidly as the first time. After the light was switched off the density fell for a short time below the stable minimum value before starting to increase. This phenomenon could easily be reproduced, but it was difficult to explain it. It may be due to the imperfection of the measuring apparatus in which there was a considerable distance between the slit and the photocell caused by the combination of the ordinary cell compartment and the fluorescence accessory set. This defect has also been described by, for example, Gibson and Balcom (1947). Therefore, if we want to perform the colour reaction under the conditions of maximum sensitivity, the

* $d = \log \frac{I_0}{I}$; I_0 = intensity of light transmitted through benzidine solution, I = intensity of light transmitted through reaction mixture.

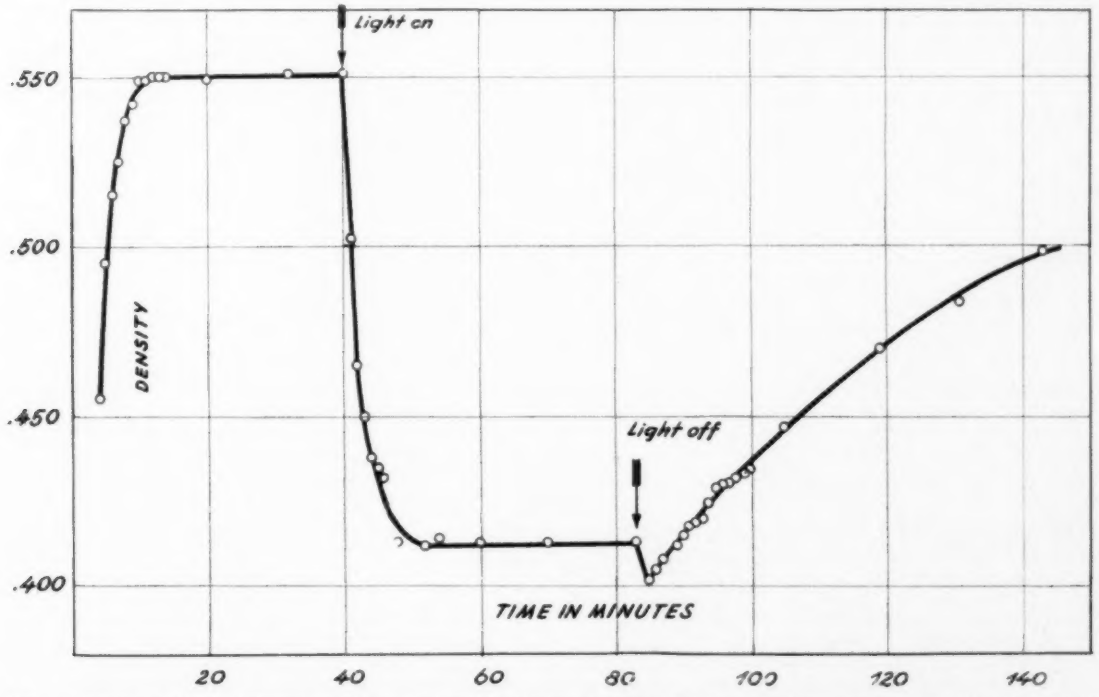


FIG. 1.—Graph showing the influence of light on the intensity of colour reaction: benzidine—tetranitromethane. Reaction mixture: 6·9 μg./ml. T.N.M. + benzidine 0·04 mg./ml. Adapted Beckman spectrophotometer with $\lambda = 400$ mμ; slit 0·06 mm.

light should be excluded. The measurement of density should not be performed earlier than 15 to 20 minutes after the reaction components are brought together.

Influence of Benzidine Concentration

If the concentration of benzidine is increased, the density of the reaction mixture also increases until an optimum concentration of benzidine is reached. A further increase in the benzidine concentration has a much smaller effect on density. This course is shown on Fig. 2 for two different T.N.M. concentrations. The optimum concentration of T.N.M. varies a little with the concentration of benzidine, but for the range of T.N.M. concentrations investigated (0–15 μg./ml.), the optimum concentration of benzidine can be assumed to be 0·2 g./litre. The greater the concentration of benzidine, the shorter is the time interval necessary for density to reach its constant value.

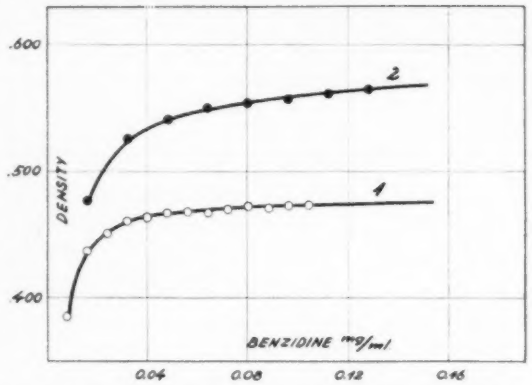


FIG. 2.—Graph showing the influence of benzidine concentration. Curve 1 relates to T.N.M. concentration of 6·0 μg./ml. Curve 2 relates to T.N.M. concentration of 10·0 μg./ml. Plotting increment for the abscissae of curve 2 is − 0·200. Beckman spectrophotometer with λ = 400 mμ ; slit 0·06 mm.

Calibration Curves

Fig. 3 shows the calibration curves for three different photometers. The calibration curves are straight lines as required by Lambert-Beer's law. The Beckman spectrophotometer gives the highest rate of increase of density with concentration of T.N.M. (straight line No. 1). The linear relation between density and concentration can be described by the equation

$$d = 0{\cdot}0808\ c$$

where $d = \log I_0/I$ = density and c = concentration of T.N.M. in mg./litre.

The light transmission of the coloured solution was measured relative to the solution of benzidine

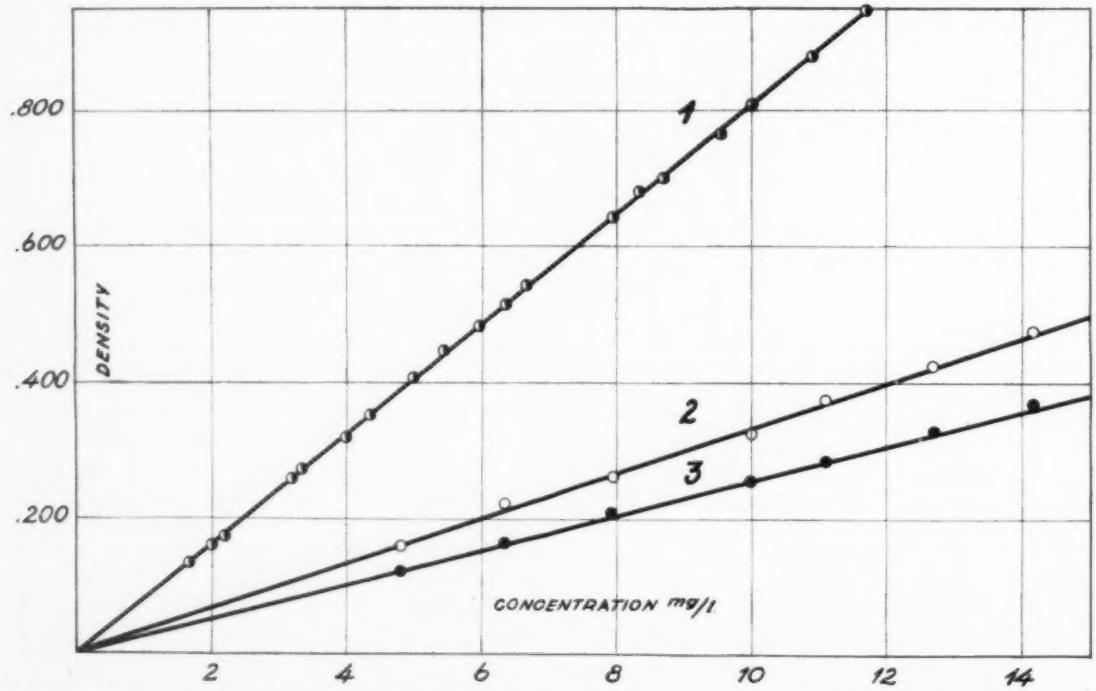


FIG. 3.—Calibrating curves for three different types of photometer. 1 = Beckman spectrophotometer with λ = 400 mμ, slit 0·06 mm.; 2 = Fisher electrophotometer, Model A.C. with light filter B (425 mμ) ; 3 = Pulfrich photometer with filter K–8a–VI (blue).

(0·2 g./litre). The constant in the equation was calculated by the least squares method the additional condition being that the straight line should pass through the origin. The probable error of the constant was found to be 0·00027 or 0·34%. The wavelength of light was 400 mμ, the slit 0·06 mm. This wavelength was chosen because the density of the coloured solution is high enough, while the density of benzidine solution is still negligibly small at this wavelength. For longer wavelengths the intensity of the colour reaction decreases rather rapidly, and hence the sensitivity of the method becomes less. For shorter wavelengths the density of the benzidine solution becomes very high.

Straight line No. 2 on the same figure shows the relation between the concentration and the density for the Fisher electrophotometer. The straight line is not so steep (d = 0·0332 c), and consequently the sensitivity of the method is less. This is probably due to the longer wavelength at which the measurements were performed (425 mμ) and the greater band width transmitted through the filter on the one hand, and to the influence of light on the intensity of the colour reaction on the other. The measurement of the transmission of light takes longer and therefore the reaction mixture is exposed to light for longer periods (see Fig. 1).

The worst results were obtained with the Pulfrich photometer (straight line No. 3). The reasons are the same as for the Fisher instrument. Owing to the design of the apparatus the densities measured are in fact the minimum values on the curve of Fig. 1 corresponding to the colour reaction developed in light. The constant in the equation is 0·0256.

The ratios of the constants for these three photometers are

$$0{\cdot}0808 : 0{\cdot}0332 : 0{\cdot}0256 = 3{\cdot}16 : 1{\cdot}3 : 1$$

Thus the method is three times more sensitive if the measurements of density are performed with the Beckman photometer in darkness than if the density is measured with the Pulfrich photometer in light. In other words, with the Beckman spectrophotometer differences in concentration of T.N.M. of 0·1 μg./ml. can be registered with precision, while with the Fisher or Pulfrich instruments differences should be three to five times as large (the error of a single measurement of density being also larger than 0·003).

Influence of Ageing of the T.N.M. Solution

For analytical practice it is important to know whether the analysis of samples should be performed

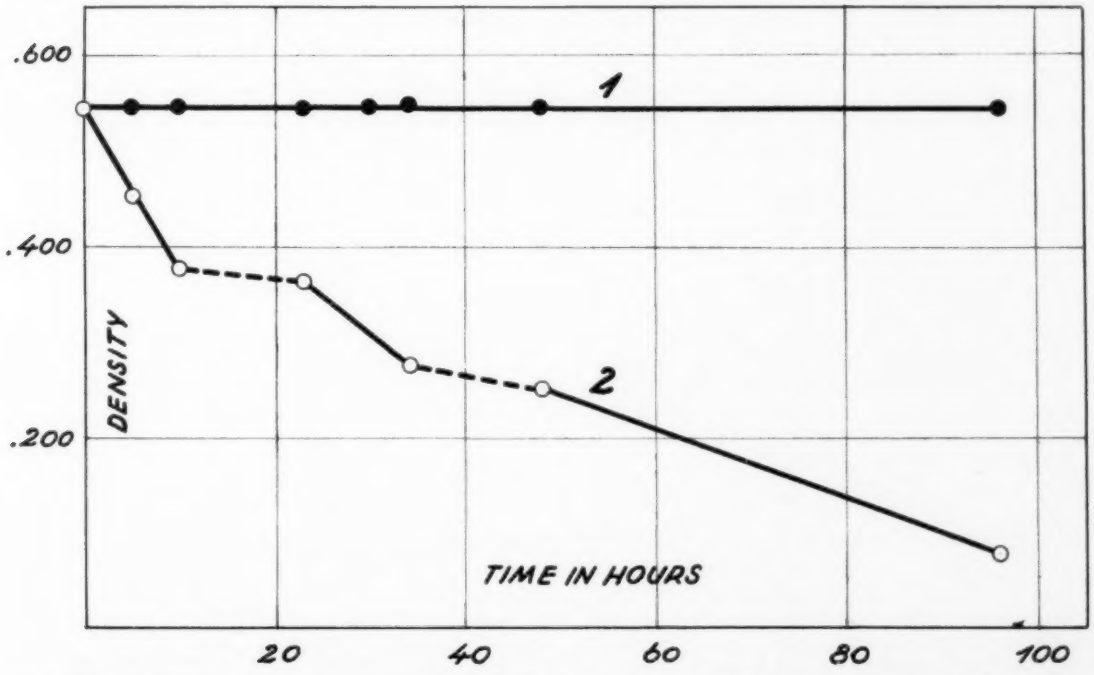


FIG. 4.—Graph showing the influence of ageing of T.N.M. solution. Curve 1 denotes density of reaction mixtures prepared with T.N.M. solution kept in darkness; abscissa denotes the age of the T.N.M. solution. Curve 2 denotes density of reaction mixtures prepared with T.N.M. solution exposed to light.

immediately. The influence of ageing of the T.N.M. solution in ethanol is shown in Fig. 4.

Curve 1 shows the change in the density of the coloured solution with ageing of the T.N.M. solution used for carrying out the reaction if the T.N.M. solution is kept in darkness. The results show that in this case the age of the T.N.M. solution has no influence. However, if the T.N.M. solution is exposed to light the intensity of the colour reaction decreases with the ageing of the T.N.M. solution (Curve 2). These findings differ from Kranz and Štepanek's observations that the T.N.M. solution in ethanol changes when exposed to light only if potassium iodide is present. This curve also shows that the change in the T.N.M. solution is slowed down during the night (dotted parts of the curve).

The benzidine solution also changes when left standing in light. This is a well known fact.

Sampling

We investigated also the influence of the sampling rate and the concentration of T.N.M. in air on the absorption of T.N.M. in alcohol. The results are given in Table 1. Two or three midget-impingers connected in series and each filled with 10 ml. of ethanol served as absorption vessels. The influence of the sampling rate on the absorption capacity of alcohol is marked. The greater the sampling rate, the less T.N.M. is retained in the first impinger. If the concentration of T.N.M. in air does not exceed 25 p.p.m., and the sampling rate is about 0·5 litres/min., impinger I retains 98·6% of the total amount of T.N.M. At T.N.M. concentrations of 80 p.p.m. and sampling rates of 1·35, approximately 6% of T.N.M. goes in the second impinger. For high concentrations and sampling velocities a third impinger should be included in the sampling set.

However, such extreme concentrations never occur in practice. Therefore, it is certainly true that for all practical purposes two impingers filled with 10 ml. ethanol each represent a good trap for T.N.M. vapours.

During sampling the room temperature was 25° C.

TABLE 1

DISTRIBUTION OF TETRANITROMETHANE (T.N.M.) IN A SERIES OF THREE IMPINGERS FILLED WITH ETHANOL

Sample No.	Tetranitromethane Concentration in Air*		Sampling		Amount in Impinger (%)		
	(mg./l.)	(p.p.m.)	Rate (l./min.)	Volume (l.)	I	II	III
1	0·18	22·3	0·428	1·0	98·4	1·6	—
2	0·18	22·3	0·428	1·0	98·4	1·6	—
3	0·17	21·5	0·428	1·0	98·8	1·2	—
4	0·17	21·0	0·428	1·0	99·0	1·0	—
				Average	98·6	1·4	
5	0·56	70·5	1·0	1·0	96·0	4·0	0·0
6	0·66	82·4	1·0	1·0	93·4	6·6	—
7	0·65	81·0	1·0	1·0	95·0	5·0	—
8	0·34	43·0	1·0	1·0	93·2	7·8	—
9	0·32	39·8	1·0	2·0	94·1	5·9	—
10	0·34	42·4	1·0	2·0	93·0	7·0	—
11	0·33	41·7	1·0	2·0	94·6	5·4	—
				Average	94·2	5·8	
12	0·73	90·7	1·35	1·35	94·7	5·3	—
13	0·68	86·0	1·35	1·35	93·5	6·5	—
14	0·65	80·2	1·35	1·35	94·5	5·5	—
15	0·63	78·6	1·35	1·35	94·8	5·2	—
16	0·61	78·2	1·35	1·35	93·5	6·5	—
				Average	94·4	5·6	
17	0·67	84·3	2·1	2·1	92·2	7·8	—
18	0·43	53·5	2·2	4·4	91·5	8·5	—
19	0·63	78·4	3·25	3·25	91·9	8·1	—
20	0·32	40·3	3·75	3·75	91·4	7·0	1·6
21	0·39	48·4	4·1	8·2	92·8	6·5	0·6
22	0·41	51·5	4·1	4·1	89·7	9·2	1·1
23	0·49	61·6	4·85	4·85	90·1	9·9	—

* As calculated from the total amount of T.N.M. found in the impingers.

The Influence of Other Contaminants

With regard to the influence of other contaminants, our results tally well with the results obtained by Sievers and others (1947). Nitrobenzene, p-nitrotoluene, toluene, xylene, benzene, $NaNO_2$ and HNO_3 in molar concentration 50 times larger than the molar concentration of T.N.M. have no appreciable influence on the intensity of colour reaction (Table 2). The only exception is p-nitrophenol which exerts a greater influence. However, such an excess of this contaminant is not likely to be encountered in field measurements.

Analysis.—An aliquot volume (1 to 9 ml.) of T.N.M. solution depending upon the concentration of T.N.M. vapours in air is pipetted in a measuring flask of 25 ml. and the *p*H of the solution brought to 6 by adding the necessary amount of purest pyridine. (*p*H may be estimated by nitrazine paper manufactured by E. R. Squibb and Sons, New York.) Benzidine solution, 5 ml., (1 g. purest benzidine dissolved in 1 litre of redistilled alcohol freshly prepared or kept in a dark place) is then added and the mixture made up to 25 ml. with ethanol. All these operations should be performed in darkness. The reaction mixture prepared in this way should be left to stand in a dark place for at least 15 to 20 minutes. The density of the mixture is then measured with a Beckman spectrophotometer at $\lambda = 400$ mμ, slit 0·06 mm.; the standard for comparison is a solution containing 0·2 mg. of benzidine in 1 ml. of ethanol.

The concentration of tetranitromethane in the solution is read from the diagram (Fig. 3) or calculated from the equation $c = 12{\cdot}4\ d$.

If this procedure is followed closely, T.N.M. in amounts of 2 μg. per millilitre can be determined with a probable error of not more than 1·3%. Hence the maximum air sample necessary for precisely determining T.N.M. in industrial air (maximum allowable concentrations ~ 0·5 p.p.m.) is 5 litres, when the volume of the absorption liquid is not more than 10 ml.

TABLE 2

INFLUENCE OF CONTAMINANTS ON INTENSITY OF COLOUR REACTION: TETRANITROMETHANE—BENZIDINE

Concentration of Contaminants (mg./25 ml.)		Density (Extinction) of the Reaction Mixture + Contaminant			
		Ethanol	0·2 ml. Pyridine 5·0 ml. Benzidine Ethanol ad 25 ml.	0·2 ml. Pyridine 7×10^{-7} gmoles T.N.M. Ethanol ad 25 ml.	0·2 ml. Pyridine 7×10^{-7} gmoles T.N.M. 5·0 ml. Benzidine Ethanol ad 25 ml.
—	—	0·000	0·011	0·002	0·518
Nitrobenzene ..	0·43	0·012	0·026	0·018	0·548
p-Nitrophenol ..	0·49	0·151	0·278	0·454	0·640
p-Nitrotoluene ..	0·48	0·020	0·041	0·026	0·544
Toluene	0·32	0·000	0·014	0·004	0·522
Xylene	0·37	0·003	0·028	0·008	0·538
Benzene	0·27	0·010	0·022	0·006	0·533
$NaNO_2$	0·24	0·007	0·027	0·017	0·507
HNO_3*	0·22	0·010	0·039	0·007	0·517

* The concentration of pyridine in the reaction mixture + HNO_3 was 3·2 vol.%.

Conclusion

In view of all these results we may state that the Sievers reaction with some modifications may serve as an excellent method for determining small amounts of T.N.M. in air. We propose the following modified procedure.

Modified Procedure

Sampling.—The air is aspirated through a set of two midget impingers each filled with 10 ml. of redistilled commercial ethanol connected in series. On the available data, it is suggested that the sampling rate should not exceed 1·0 litre per minute. As soon as the sampling is completed, the impingers with T.N.M. solution should be put in a dark place.

References

Baillie, A., Macbeth, A. K., and Maxwell, N. J. (1920). *J. Chem. Soc.*, **117**, 880.

Cruse, K., and Haul, R. (1949). *Z. Elektrochem.*, **53**, 115.

Ehrenberg, L., Fisher, I., and Löfgren, N. (1945). *Svensk. Kem. Tid.*, **57**, 303.

Elkins, H. P. (1950). "The Chemistry of Industrial Toxicology." New York.

Gibson, K. S., and Balcom, M. M. (1947). U.S. Department of Commerce National Bureau of Standards Research Paper, **38**, 1798.

Kranz, C. K. and Štepanek, J. M. (1937). *Chem. Obzor.*, **12**, 85.

Poe Liang (1941). Org. Syntheses, **21**, 105–7.

Reid, E. W., and Hoffmann, H. E. (1929). *Ind. Eng. Chem.*, **21**, 695.

Scott, E. W. (1943). *J. ind. Hyg. Toxicol.*, **25**, 20.

Sievers, R. F., Rushing, E., Gay, H., and Monaco, A. R. (1947). *U.S. Public Health Reports*, **62**, 1048.

Brit. J. industr. Med., 1952, **9**, 39.

CONTRIBUTION A L'ETUDE DE LA TOXICOLOGIE DU TRICHLORETHYLENE

II. RESULTATS DES ETUDES EXPERIMENTALES CHEZ L'ANIMAL

PAR

RENÉ FABRE et RENÉ TRUHAUT

Du Laboratoire de Toxicologie de la Faculté de Pharmacie de Paris

Ayant établi une méthode de dosage du trichloréthylène et de son produit de transformation métabolique, l'acide trichloracétique, dans les milieux biologiques, nous avons entrepris l'étude de l'intoxication expérimentale par le trichloréthylène. Nous avons pu ainsi apporter un certain nombre de précisions relatives à cette intoxication : localisations du solvant et de son métabolite dans les divers organes, répartition érythro-plasmatique, rythme d'élimination, organes de transformation du trichloréthylène en acide trichloracétique, modalités de cette transformation*.

Localisations dans l'Intoxication Chronique.—Des cobayes ont été soumis, en cage respiratoire, à des inhalations répétées d'air chargé de trichloréthylène à faible concentration. (La concentration dans l'atmosphère était assurée de façon homogène grâce au dispositif classique de mélange de vapeurs de solvant et d'air.) Les animaux ont été sacrifiés et leurs organes ou humeurs prélevés, pesés, et conservés à la glacière en vue du dosage du toxique et de son métabolite.

Cobaye No. 1.—Inhalation pendant cinq jours, à raison de quatre heures par jour, d'une atmosphère à 9 mg. de trichloréthylène par litre.

Cobaye No. 2.—Inhalation pendant 13 jours, à raison de quatre heures 30 par jour, d'une atmosphère à 6 mg. de trichloréthylène par litre.

Cobaye No. 3.—Inhalation pendant 19 jours, à raison de cinq heures par jour, d'une atmosphère à 6 mg. de trichloréthylène par litre.

Cobaye No. 4.—Inhalation pendant 23 jours, à raison de cinq heures 15 par jour, d'une atmosphère à 7 mg. de trichloréthylène par litre.

Les résultats sont consignés dans les deux tableaux suivants (Tableaux 1 et 2).

L'examen des chiffres montre que le trichloréthylène diffuse dans tous les organes qui en renferment des taux notables. Il y a donc imprégnation profonde de tout l'organisme. Si l'on classe les tissus d'après les teneurs observées, en commençant par les plus faibles, on obtient l'ordre suivant ; pour le trichloréthylène : muscle, foie, cerveau, sang, poumon, rate, rein, surrénale ; pour l'acide trichloracétique : foie, cerveau, rein, sang, poumon, rate, surrénale.

Ainsi, aussi bien pour l'acide trichloracétique que pour le trichloréthylène, les taux les plus élevés s'observent dans les glandes endocrines (surrénales et glandes génitales en particulier) la rate, le rein, le poumon, les réserves adipeuses et le cerveau, cette dernière localisation rendant compte des symptômes nerveux observés.

Localisations dans l'Intoxication Massive.—Un cobaye a été soumis à l'inhalation d'une atmosphère saturée de vapeurs de trichloréthylène, le premier jour pendant deux heures, le second jour pendant quatre heures, ce qui a provoqué une anesthésie totale au cours de laquelle l'animal a été sacrifié. Nous avons obtenu les résultats suivants (Tableau No. 3).

La quantité de trichloréthylène retrouvée est naturellement beaucoup plus grande que dans les cas précédents. Mais le taux d'acide trichloracétique est sensiblement le même dans les deux modes d'intoxication, ce qui tendrait à prouver que l'excès de trichloréthylène inhalé n'a pas eu le temps de subir de transformation et, par suite, n'a pas élevé le taux du métabolite dans les organes.

Repartition Erythroplasmatique.—Elle a été étudiée chez le rat. Cinq animaux ont été soumis à l'inhalation d'une

* Les premiers résultats de ce travail ont été obtenus avec la collaboration de Melle de Belvata Balasy qui a effectué sur ce sujet une thèse de Doctorat en Pharmacie à notre laboratoire (de Belvata Balasy "Contribution à l'étude du trichloréthylène de son élimination, de sa localisation et de son métabolisme dans l'organisme", Paris, 1949).

TABLEAU No. 1

RÉPARTITION DU TRICHLORÉTHYLÈNE DANS LES TISSUS OU HUMEURS DU COBAYE AU COURS DE L'INTOXICATION CHRONIQUE

Tissu ou humeur	Cobaye No. 1	Cobaye No. 2	Cobaye No. 3	Cobaye No. 4
Cerveau ..	0,5	0,7	0,9	1
Foie	0,8	0,5	1	0,56
Tissu adipeux..	3,1	3,5	3,9	3,8
Muscle ..	—	0,5	0,21	0,24
Ovaires ..	—	2,3	2,3	—
Poumons ..	0,8	1,2	0,7	0,8
Rate	1,7	1,9	1,3	0,9
Reins	2,2	0,8	1,4	1,8
Surrénales ..	—	3,4	2,2	3,8
Sang	1,3	1	0,5	0,78
Urine		3,5	3,1	2,6

(Taux en m. 100 g. de matière fraiche)

TABLEAU No. 2

RÉPARTITION DE L'ACIDE TRICHLORACÉTIQUE DANS LES TISSUS OU HUMEURS DU COBAYE AU COURS DE L'INTOXICATION CHRONIQUE

Tissu ou humeur	Cobaye No. 1	Cobaye No. 2	Cobaye No. 3	Cobaye No. 4
Cerveau ..	3,2	3	2,5	3
Foie	2,8	2	1,2	1,1
Tissu adipeux..	4,4	—	3,5	—
Ovaires ..	—	7	8	—
Poumons ..	4,2	3,3	3,2	3,2
Rate	9,3	9	8,6	7,8
Rein	4,	3,4	2,1	—
Surrénales ..	—	12	11	10
Sang	3,6	3,75	3,1	2,7
Urine	—	5	4,8	4,7

(Taux en mg. 100 g. de matière fraiche)

TABLEAU No. 3

RÉPARTITION DU TRICHLORÉTHYLÈNE DANS LES TISSUS DU COBAYE AU COURS DE L'INTOXICATION MASSIVE

Organes	Trichloréthylène (mg./100 g.)	Acide Trichloracétique (mg./100 g.)
Cerveau ..	16	2,5
Foie	—	2
Graisse ..	14	—
Poumons ..	—	3,6
Rate	8, 75	6,6
Surrénales ..	20	—

atmosphère renfermant 4 mg. par litre de trichloréthylène (atmosphère 1), deux heures par jour pendant un certain nombre de jours variable avec les animaux, après quoi, ils ont subi l'inhalation d'une atmosphère à 10 mg. par litre (atmosphère 2) entraînant l'anesthésie, puis, ils ont été sacrifiés par saignée à blanc. Le sang recueilli sur fluorure de sodium a été immédiatement centrifugé à grande vitesse et le plasma et les globules ont été soumis séparément à la double détermination du trichloréthylène et de l'acide trichloracétique.

Rat No 1.—Inhalation pendant deux heures de l'atmosphère 1 ; le lendemain, inhalation pendant une heure de l'atmosphère 2.

Rats Nos. 2 *et* 3.—Inhalation deux heures par jour, pendant trois jours, de l'atmosphère 1 ; le quatrième jour, inhalation pendant une heure de l'atmosphère 2.

Rat No. 4.—Intoxication comme pour les rats Nos. 2 et 3, mais, à la suite de la dernière inhalation, l'animal a été laissé au repos 24 heures avant d'être sacrifié.

Rat No. 5.—Inhalation deux heures par jour, pendant quatre jours de l'atmosphère 1 ; à la suite de la dernière inhalation, l'animal a été laissé au repos 48 heures avant d'être sacrifié.

Voici les résultats obtenus (Tableau No. 4).

TABLEAU No. 4

RÉPARTITION ÉRYTHROPLASMATIQUE DANS L'INTOXICATION LENTE PAR LE TRICHLORÉTHYLÈNE CHEZ LE RAT

	Trichloréthylène (mg./100 g.)	Acide Trichloracétique (mg./100 g.)
Rat No. 1		
Globules ..	41,3	10
Plasma ..	2,5	2,4
Rapport G/P	16	4
Rat No. 2		
Globules ..	91	12
Plasma ..	5,6	5,4
Rapport G/P	16	2,2
Rat No. 3		
Globules ..	73–75	12,75
Plasma ..	4,7	4,4
Rapport G/P	15,6	2,8
Rat No. 4		
Globules ..	13	6
Plasma ..	2	6
Rapport G/P	6	1
Rat No. 5		
Globules ..	2	6,5
Plasma ..	1,2	6
Rapport G/P	1,6	1

Ces chiffres démontrent d'une façon évidente la fixation élective du trichloréthylène et, à un moindre degré, de l'acide trichloracétique sur les globules rouges. Cette fixation élective qui découle logiquement de l'affinité pour les lipides, que traduisent en outre les symptômes nerveux de l'intoxication, explique l'accumulation splénique (rate réservoir de globules rouges) ; elle doit, par ailleurs, intervenir pour ralentir l'élimination du toxique et de son métabolite.

Evolution de la Transformation du Trichloréthylène en Acide Trichloracetique.—Nous avons dosé dans les principaux organes des rats précédents le trichloréthylène et son métabolite. Les chiffres obtenus sont consignés dans les deux tableaux suivants (Tableaux 5 et 6).

TABLEAU No. 5

RÉPARTITION DU TRICHLORÉTHYLÈNE DANS LES TISSUS DU RAT AU COURS D'INTOXICATIONS LENTES

Organes	Rat No. 1	Rat No. 2	Rat No. 4	Rat No. 5
Cerveau ..	5	12,8	2,2	—
Foie	8,5	10	6,75	3,5
Poumons ..	9	8,5	1,3	1
Rate	9	14	14	8
Reins	4,5	5,9	3	—

(Taux en mg. 100 g. de matière fraiche)

TABLEAU No. 6

RÉPARTITION DE L'ACIDE TRICHLORACÉTIQUE DANS LES TISSUS DU RAT AU COURS D'INTOXICATIONS LENTES

Organes	Rat No. 1	Rat No. 2	Rat No. 4	Rat No. 5
Cerveau ..	2,5	2,5	2,4	—
Foie	2,6	2,6	4	5
Poumons ..	4,5	3	2,7	4,3
Rate	6,4	6	5,4	10
Reins	2,3	2,1	—	—

(Taux en mg. 100 g. de matière fraiche)

On voit que se vérifie sur le rat la notion établie sur le cobaye de la diffusion dans tous les organes du trichloréthylène inhalé. Il subit, dans certains d'entre eux, une transformation en acide trichloracétique dont le taux augmente progressivement après la suppression de la cause d'intoxication.

Elimination de l'Acide Trichloracétique Absorbé par Voie Buccale.—L'acide trichloracétique, formé à la suite d'une intoxication au trichloréthylène, s'élimine lentement. D'après Powell (1945), la production est maximal en 48 heures et se poursuit pendant 10 à 12 jours. Les auteurs suédois Ahlmark et Forssman (1948) ont également insisté sur l'élimination retardée de ce métabolite.

Nous avons personnellement effectué quelques recherches pour préciser le rythme de cette élimination. Nous avons administré à des cobayes 0 g 01 d'acide trichloracétique en solution aqueuse neutralisée par le bicarbonate de sodium et nous avons pu montrer que son élimination dans ces conditions était beaucoup plus rapide (deux jours au lieu de six à huit jours) que celle de l'acide formé dans le métabolisme du trichloréthylène. Ce résultat était prévisible, car il faut que soit réalisée au préalable l'accumulation du solvant dans les organes de transformation et, par ailleurs, cette dernière n'est évidemment pas immédiate, mais progressive.

Les Organes de Transformation du Trichloréthylène en Acide Trichloracétique : Ses Modalités.—Après avoir étudié les localisations du trichloréthylène et de l'acide trichloracétique et précisé les conditions d'élimination de ce dernier, nous avons essayé de mettre en évidence le ou les organes dans lesquels s'effectue la transformation du trichloréthylène. Dans ce but, nous avons effectué successivement des expériences *in vitro* et *in vivo*.

Pour les expériences *in vitro*, nous avons utilisé des rats blancs normaux de poids moyen de 200 g., qui ont été sacrifiés et dont nous avons prélevé immédiatement les organes. Ceux-ci, additionnés de doses variables de trichloréthylène en solution aqueuse dans des flacons bouchant à l'émeri, ont été portés à l'étuve à 37°, pendant une durée variant d'une demi-heure à huit heures. Puis nous avons dosé le trichloréthylène résiduel et l'acide trichloracétique apparu.

La technique adoptée a été la suivante : on prépare tout d'abord une solution de trichloréthylène dans l'eau distillée à la concentration de 220γ par cm.3 et une solution aqueuse saturée de toluène, cette dernière destinée à éviter les phénomènes de putréfaction.

On pèse l'organe ou une portion d'organe, on le pulpe au sein d'un faible volume de soluté physiologique (5 cm.3 pour 1 g. d'organe), on transvase dans un flacon bouchant à l'émeri, on ajoute 1 cm.3 de solution de trichloréthylène et 0, 50 cm.3 de solution toluénique, on bouche, on agite, on porte le flacon à l'étuve à 37° et on l'y maintient le temps prévu. On place ensuite l'échantillon à la glacière pour suspendre les actions fermentaires et on procède au dosage.

Nous avons réuni les résultats obtenus dans le tableau No. 7.

On voit que la transformation du trichloréthylène en acide trichloracétique augmente avec la durée de séjour à l'étuve. Le maximum semble être atteint

TABLEAU NO. 7

TRANSFORMATION DU TRICHLORÉTHYLÈNE EN ACIDE TRICHLORACÉTIQUE DANS LES ORGANES *in vitro**

Temps de Sejour à l'étuve á 37°	1/2 h	3/4 h	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
Cerveau ..	0	0	0	0	traces	80	73	—	64	54
Foie	0	0	traces	traces	31	20	36	47	69	43
Poumons ..	0	0	0	0	42	68	182	112	62	60
Rate	0	traces	traces	traces	62	132	171	200	150	112
Reins	0	traces	traces	traces	50	—	85	—	45	55

* Quantites d'acide trichloracétique en γ ramenees à 2 g. d'organe frais (rats).

aprés cinq à six heures. Les organes qui sont le plus actifs sont la rate et les poumons, le foie ne venant qu'en troisième ligne.

Pour les expériences *in vivo*, au lieu de mettre en contact des organes d'animaux normaux avec une solution de trichloréthylène, nous avons placé à l'étuve en flacons bouchés des organes provenant d'animaux soumis à l'inhalation d'air chargé de trichloréthylène ; quatre expériences ont été réalisées sur des foies et rates de cobayes et de rats.

Elles nous ont permis d'observer une formation supplémentaire d'acide trichloracétique qui traduit la continuation du processus métabolique déjà commencé *in vivo*.

Nous avons enfin étudié l'influence sur ce processus métabolique, d'une part de la concentration en trichloréthylène, d'autre part du fluorure de sodium dont on sait l'action inhibitrice sur toute une série de processus enzymatiques.

Des pulpes d'organes ont été mises en contact pendant quatre heures à l'étuve à 37° avec des solutions de trichloréthylène à des titres divers (160γ/cm.3 et 320γ/cm.3). A la fin de l'expérience, le trichloréthylène restant et l'acide trichloracétique opparu ont été dosés. Les chiffres obtenus montrent que la formation d'acide trichloracétique semble, dans une certaine mesure, indépendante de la concentration en trichloréthylène comme s'il existait une limite au pouvoir de transformation des tissus (Tableau No. 8).

Ainsi se trouve légitimée l'utilisation de ce produit pour le prélèvement des échantillons de sang en vue du dosage du trichloréthylène et de l'acide trichloracétique.

Conclusions

A l'aide de la méthode antérieurement établie pour le dosage du trichloréthylène et de son produit de transformation métabolique l'acide trichloracétique, nous avons abordé l'étude de l'intoxication expérimentale aiguë ou chronique par le trichloréthylène chez l'animal (rat, cobaye).

Nous avons tout d'abord mis en évidence la fixation importante aussi bien du trichloréthylène que de l'acide trichloracétique dans les glandes endocrines (surrénales et glandes génitales en particulier), la rate, le sang, le rein, le poumon, et le cerveau. Cette dernière localisation cadre avec les symptômes nerveux observés dans l'intoxication. Dans le cas du sang, l'étude de la répartion globulo-plasmatique nous a permis de démontrer l'affinité du toxique et, à un moindre degré, de l'acide trichloracétique pour les globules rouges. Cette fixation élective qui découle de l'affinité pour les lipides, explique l'accumulation splénique (rate réservoir de globules rouges).

TABLEAU NO. 8

ETUDE DE L'INFLUENCE DE LA CONCENTRATION EN TRICHLORÉTHYLÈNE SUR LA TRANSFORMATION EN ACIDE TRICHLORACÉTIQUE PAR DES PULPES D'ORGANES *in vitro*

Organes (Rat)	Prélèvement en g.	Temps de séjour à 37°	Trichloréthylène Ajouté en γ	Acide Trichloracétique Apparu en γ
Foie	3	3 h.	320	57
Foie	3	5 h.	160	55
Rate..	0,4	3 h. 30	320	25
Rate..	0,4	3 h. 30	160	28
Reins	0,8	5 h.	320	20
Reins	0,8	5 h.	160	28

Pour étudier l'action du fluorure de sodium, nous avons opéré avec de la pulpe de foie provenant d'un cobaye ayant respiré une atmosphère concentrée de trichloréthylène jusqu'à anesthésie. Nous avons fait trois expériences simultanées : pulpe témoin placée immédiatement à 0° ; pulpe témoin additionnée de 0,5 cm.3 de solution toluénique et placée 4 h. 15 à l'étuve à 37° en flacon bouché ; et pulpe additionnée de quantités croissantes d'une solution de fluorure de sodium à 500γ/cm.3 et placée à l'étuve à 37° en flacon bouché.

Sur ces différentes pulpes, nous avons dosé le trichloréthylène et l'acide trichloracétique.

Les chiffres obtenus nous ont montré que le fluorure de sodium à la concentration de 50γ pour 2 g. d'organe exerce une action retardatrice sur la transformation du trichloréthylène en acide trichloracétique.

Par utilisation de pulpes d'organes, nous avons pu démontrer que, dans la transformation métabolique en acide trichloracétique, les tissus splénique et pulmonaire ont un rôle prépondérant, nettement supérieur en particulier à celui du tissu hépatique. Nous n'avons pu élucider le mécanisme exact de cette transformation curieuse à plus d'un titre, mais, en revanche, nous avons pu montrer que le fluorure de sodium exerçait vis à vis d'elle une influence inhibitrice, légitimant ainsi l'emploi de ce composé pour les prélèvements destinés à l'analyse toxicologique.

Du point de vue de l'élimination, alors que, chez l'homme comme chez l'animal, celle du trichloréthylène s'effectue rapidement par l'air

expiré et l'urine, celle de l'acide trichloracétique, exclusivement urinaire, est plus lente et persiste plusieurs jours après la suppression de la cause d'intoxication. Il constitue par suite un véritable indicateur d'exposition. L'intérêt de sa recherche et de son dosage dans l'urine pour le dépistage des intoxications professionnelles, déjà souligné par les auteurs suédois Ahlmark et Forssman (1948, 1951), se trouve ainsi confirmé.

BIBLIOGRAPHIE

Ahlmark, A., et Forssman, S. Proceedings of the ninth international congress on Industrial Medicine, London, September 1948. Wright, Bristol, 1949 ; pp. 552-53 ; (1951) *Arch. industr. Hyg. occup. Med.*, **3**, 386.

Fabre, R., et Truhaut, R. (1951). *British Journal of Industrial Medicine*, **8**, 275.

Powell, J. F. (1945). *Ibid.*, **2**, 142.

aprés cinq à six heures. Les organes qui sont le plus actifs sont la rate et les poumons, le foie ne venant qu'en troisième ligne.

Pour les expériences *in vivo*, au lieu de mettre en contact des organes d'animaux normaux avec une solution de trichloréthylène, nous avons placé à l'étuve en flacons bouchés des organes provenant d'animaux soumis à l'inhalation d'air chargé de trichloréthylène ; quatre expériences ont été réalisées sur des foies et rates de cobayes et de rats.

Elles nous ont permis d'observer une formation supplémentaire d'acide trichloracétique qui traduit la continuation du processus métabolique déjà commencé *in vivo*.

Nous avons enfin étudié l'influence sur ce processus métabolique, d'une part de la concentration en trichloréthylène, d'autre part du fluorure de sodium dont on sait l'action inhibitrice sur toute une série de processus enzymatiques.

Des pulpes d'organes ont été mises en contact pendant quatre heures à l'étuve à 37° avec des solutions de trichloréthylène à des titres divers (160γ/cm.3 et 320γ/cm.3). A la fin de l'expérience, le trichloréthylène restant et l'acide trichloracétique opparu ont été dosés. Les chiffres obtenus montrent que la formation d'acide trichloracétique semble, dans une certaine mesure, indépendante de la concentration en trichloréthylène comme s'il existait une limite au pouvoir de transformation des tissus (Tableau No. 8).

Ainsi se trouve légitimée l'utilisation de ce produit pour le prélèvement des échantillons de sang en vue du dosage du trichloréthylène et de l'acide trichloracétique.

Conclusions

A l'aide de la méthode antérieurement établie pour le dosage du trichloréthylène et de son produit de transformation métabolique l'acide trichloracétique, nous avons abordé l'étude de l'intoxication expérimentale aiguë ou chronique par le trichloréthylène chez l'animal (rat, cobaye).

Nous avons tout d'abord mis en évidence la fixation importante aussi bien du trichloréthylène que de l'acide trichloracétique dans les glandes endocrines (surrénales et glandes génitales en particulier), la rate, le sang, le rein, le poumon, et le cerveau. Cette dernière localisation cadre avec les symptômes nerveux observés dans l'intoxication. Dans le cas du sang, l'étude de la répartion globulo-plasmatique nous a permis de démontrer l'affinité du toxique et, à un moindre degré, de l'acide trichloracétique pour les globules rouges. Cette fixation élective qui découle de l'affinité pour les lipides, explique l'accumulation splénique (rate réservoir de globules rouges).

TABLEAU NO. 8

ETUDE DE L'INFLUENCE DE LA CONCENTRATION EN TRICHLORÉTHYLÈNE SUR LA TRANSFORMATION EN ACIDE TRICHLORACÉTIQUE PAR DES PULPES D'ORGANES *in vitro*

Organes (Rat)	Prélèvement en g.	Temps de séjour à 37°	Trichloréthylène Ajouté en γ	Acide Trichloracétique Apparu en γ
Foie	3	3 h.	320	57
Foie	3	5 h.	160	55
Rate..	0,4	3 h. 30	320	25
Rate..	0,4	3 h. 30	160	28
Reins	0,8	5 h.	320	20
Reins	0,8	5 h.	160	28

Pour étudier l'action du fluorure de sodium, nous avons opéré avec de la pulpe de foie provenant d'un cobaye ayant respiré une atmosphère concentrée de trichloréthylène jusqu'à anesthésie. Nous avons fait trois expériences simultanées : pulpe témoin placée immédiatement à 0° ; pulpe témoin additionnée de 0,5 cm.3 de solution toluénique et placée 4 h. 15 à l'étuve à 37° en flacon bouché ; et pulpe additionnée de quantités croissantes d'une solution de fluorure de sodium à 500γ/cm.3 et placée à l'étuve à 37° en flacon bouché.

Sur ces différentes pulpes, nous avons dosé le trichloréthylène et l'acide trichloracétique.

Les chiffres obtenus nous ont montré que le fluorure de sodium à la concentration de 50γ pour 2 g. d'organe exerce une action retardatrice sur la transformation du trichloréthylène en acide trichloracétique.

Par utilisation de pulpes d'organes, nous avons pu démontrer que, dans la transformation métabolique en acide trichloracétique, les tissus splénique et pulmonaire ont un rôle prépondérant, nettement supérieur en particulier à celui du tissu hépatique. Nous n'avons pu élucider le mécanisme exact de cette transformation curieuse à plus d'un titre, mais, en revanche, nous avons pu montrer que le fluorure de sodium exerçait vis à vis d'elle une influence inhibitrice, légitimant ainsi l'emploi de ce composé pour les prélèvements destinés à l'analyse toxicologique.

Du point de vue de l'élimination, alors que, chez l'homme comme chez l'animal, celle du trichloréthylène s'effectue rapidement par l'air

expiré et l'urine, celle de l'acide trichloracétique, exclusivement urinaire, est plus lente et persiste plusieurs jours après la suppression de la cause d'intoxication. Il constitue par suite un véritable indicateur d'exposition. L'intérêt de sa recherche et de son dosage dans l'urine pour le dépistage des intoxications professionnelles, déjà souligné par les auteurs suédois Ahlmark et Forssman (1948, 1951), se trouve ainsi confirmé.

BIBLIOGRAPHIE

Ahlmark, A., et Forssman, S. Proceedings of the ninth international congress on Industrial Medicine, London, September 1948. Wright, Bristol, 1949 ; pp. 552–53 ; (1951) *Arch. industr. Hyg. occup. Med.*, **3**, 386.

Fabre, R., et Truhaut, R. (1951). *British Journal of Industrial Medicine*, **8**, 275.

Powell, J. F. (1945). *Ibid.*, **2**, 142.

Brit. J. industr. Med., 1952, **9**, 44.

A CLINICAL-PATHOLOGICAL REPORT OF EIGHT CASES OF METHYL BROMIDE POISONING

BY

J. H. PRAIN and G. HARVEY SMITH

From the Department of Pathology, University of St. Andrews, and Royal Infirmary, Dundee

(RECEIVED FOR PUBLICATION JULY 9, 1951)

Methyl bromide, refrigerant, fumigant, and fire extinguisher, has proved a dangerous substance. Schuler demonstrated its toxic character in 1899, and von Oettingen (1946) has listed 28 fatalities and 150 non-fatal cases of methyl bromide poisoning.

On November 4, 1947, at about 8 in the evening eight boys broke bounds from an approved school in Dundee, and despite a search by the police no trace of them was found until 8.30 the next morning when two of the boys reported back to the school stating that they felt ill. Very shortly after their return one of the boys collapsed in what appeared to be a severe epileptiform seizure (Case 1). First aid treatment by the school medical officer failed to improve his condition, and he was admitted to the Royal Infirmary, Dundee. Shortly afterwards the second boy (Case 2), who had given an incoherent story of the remaining six boys being aboard a boat in the harbour, also collapsed. He had a much milder epileptiform seizure, and was also brought to the Infirmary.

The police searched again and found the other six boys huddled together in varied degrees of unconsciousness in a small cabin aboard a disused Royal Air Force launch. These boys were also sent to the Royal Infirmary, Dundee. The police also found a recently discharged fire extinguisher of the No. 3 Air Ministry pattern which, when full, contains 69 fluid oz. of methyl bromide.

The eight cases presented a picture differing only in degree, although later some qualitative differences were appreciated.

Clinical Reports

On admission to hospital Case 1 (age 14), Case 5 (age 14), Case 6 (age 13½), and Case 7 (age 13) presented similar clinical features. All were unconscious with wide, staring eyes, a blue-grey, cold, moist skin, and had obvious signs of massive pulmonary oedema. In all the reflexes were depressed; on admission three were in convulsions, and the fourth (Case 6) developed convulsions one hour later. No urine was passed and death occurred 14 hours, one and three quarter hours, six and three quarter hours, and 14½ hours respectively after admission.

Case 4 (age 13) was semiconscious on admission, but suffered from marked mental confusion. The skin had a bluish-grey pallor and was cold and moist. Although the respiratory rate was 34 a minute, the lungs were clear, but three hours later loud, bubbling râles were present in all areas of the chest. Two hours later convulsions developed, and the boy died eight hours after admission. No urine was passed.

In all these cases intensive therapy—atropine, sedatives, oxygen, and stimulants—appeared to have no effect whatever on the general downhill course.

Case 8 (age 11½) was found to be dead on arrival at hospital.

The others, Cases 2 and 3, survived. Case 2 (age 13) was conscious and rational but very drowsy. The heart sounds were normal and the pulse of good volume and regular (100/min.). No adventitious sounds were heard in the lungs and respiration was quiet (22/min.). The reflexes were all depressed. Four hours after admission a convergent squint appeared. On admission Ringer's solution was given intravenously (20 ml. each hour), and although by evening the patient was very restless and sweating, the lungs were still clear. Next morning, 24 hours after admission, he was feeling much better.

From the time of admission he had not passed urine but there was no evidence of distension of the bladder by percussion. Throughout the second day his condition improved, but as he remained in a state of anuria he was given 1 pint of 4·3% sodium sulphate solution intravenously. Next day he again stated that he felt much better although some puffiness of the face had developed. Eventually that afternoon, 54 hours after admission, he passed 24 oz. of urine which had a specific gravity of 1010, and contained massive amounts of albumin and granular casts. Thereafter his progress was uneventful, and he was discharged one month later apparently fully recovered and has remained healthy over a period of two years.

A glucose tolerance test performed on the day before discharge from hospital showed a slight lowering of the renal threshold, but a urea concentration test on the following day gave satisfactory results.

The results of chemical investigations in this and Cases 1 and 3 are given in the appendix.

Case 3 (age 11) showed marked mental confusion but no other abnormal signs. He could understand simple questions and lay quietly in bed unless disturbed, when he became very noisy and restless. His colour was good, and no abnormal signs were found in the chest, respiration being normal (22/min.). The heart sounds were normal and the pulse was regular and of good volume. All reflexes were present but diminished. Three hours after admission his condition had deteriorated and he was very restless and confused. A few moist râles appeared in the lungs five hours later, but after a static period his condition gradually improved. The next morning breathing was a little laboured, an internal strabismus had developed, and the ophthalmologist found some pallor of the optic discs. Up to this time he had passed no urine ; the bladder was not full, but there was suprapubic tenderness. Thirty-two hours after admission he passed 4 oz. of urine, which had a specific gravity of 1020, contained considerable amounts of albumin and many granular casts with some hyaline casts and a few pus cells. For the next two days he remained drowsy but his condition improved, and he was discharged a fortnight after admission.

Four days after his admission he was talking rationally and spoke of a " dream " about being on a boat with the other boys. When seen two years after the incident, he still had no clear recollection of what had happened.

A review of the clinical features confirms the prognostic significance of generalized convulsions. The six cases developing convulsions all proved fatal. Of the two survivors one had a mild and brief epileptiform seizure, and he was obviously more ill than the boy who had no convulsive movements. Another case reported by Ramond and Lacorne (1942) recovered after convulsions, but generally their occurrence has meant a fatal outcome (Holling and Clarke, 1944 ; Gray, 1944).

The massive pulmonary oedema associated with the convulsions in the fatal cases made treatment difficult.

Two other important clinical points are the anuria shown by all the cases, and the delayed onset of symptoms in the boy who walked three and a half miles home (Case 1) and yet died of the poisoning.

It is of particular interest that phosgene poisoning, such as occurred in the 1914–18 war, was thought of by several clinicians experienced in chemical warfare before it was known that the boys had been exposed to a toxic vapour.

Necropsy Reports

Post-mortem examinations were carried out on five of the six fatal cases (Cases 1, 4, 5, 6, and 8).

Marked post-mortem lividity, scattered petechial haemorrhages, and cyanosis were seen in all cases with the exception of Case 5 in which no lividity was noticed. There was injection and congestion of the trachea and bronchi, numerous petechial haemorrhages being seen in Case 4, and in Case 6 the bronchi contained approximately 200 ml. of frothy fluid. Small, blood-stained bilateral pleural effusions were present in Cases 1 and 4. In the lungs there was congestion and pulmonary oedema in all the cases, and there were numerous subpleural haemorrhages most numerous in the interlobar fissures, while other discrete areas of haemorrhage were found throughout the lung substance. The liver and kidneys showed evidence of venous congestion. The meninges were congested and small subarachnoid haemorrhages were present. In one instance, Case 4, a subdural haemorrhage was present below the tentorium, lying chiefly in the left posterior fossa and passing downwards through the foramen magnum to the left side of the upper part of the spinal cord. The brain was congested, an occasional small cerebral haemorrhage was seen, and in one instance, Case 6, haemorrhage into the right choroid plexus had occurred.

During the examinations it was found that in Case 8 the right kidney showed multiple tuberculous foci with caseation, fibrosis, and in some parts calcification, while the left kidney showed one small fibrotic lesion of tuberculous type.

Histological Reports

Respiratory System.—The tracheae and bronchi were extremely congested and the submucosa seemed distended with blood-containing sinuses ; the mucosa itself merely showed an occasional small area of desquamation.

The picture in the lungs varied slightly from case to case, and to a certain extent with the area of lung under observation, but there was some degree of oedema in all sections. The intense staining reaction (Fig. 1) suggested a high protein content : nonetheless there were very few cells in the fluid and certainly nothing like the pneumonic change found by Mazel, Bourret, and Roche (1946) in one of their cases. The alveolar capillaries were generally distended but there was little evidence of diffuse diapedesis and none of intracapillary thrombosis. The gross haemorrhages in the subpleural areas had curiously well-defined margins, but deeper in the lungs the edges of the haemorrhages were most diffuse.

Liver.—The liver showed acute venous congestion macroscopically, but no evidence of parenchymatous damage.

Kidneys.—The kidneys were examined in all five cases, material from two being obtained within eight hours of death. Both cases had survived between 14 and 18 hours after exposure to methyl bromide vapour. In the other three cases the necropsy was delayed by legal formalities and gross autolytic change was present.

Extreme congestion was seen in the capillaries of the cortex, and tense engorgement of the stellate veins and vasa recti. In contrast, most of the glomeruli were

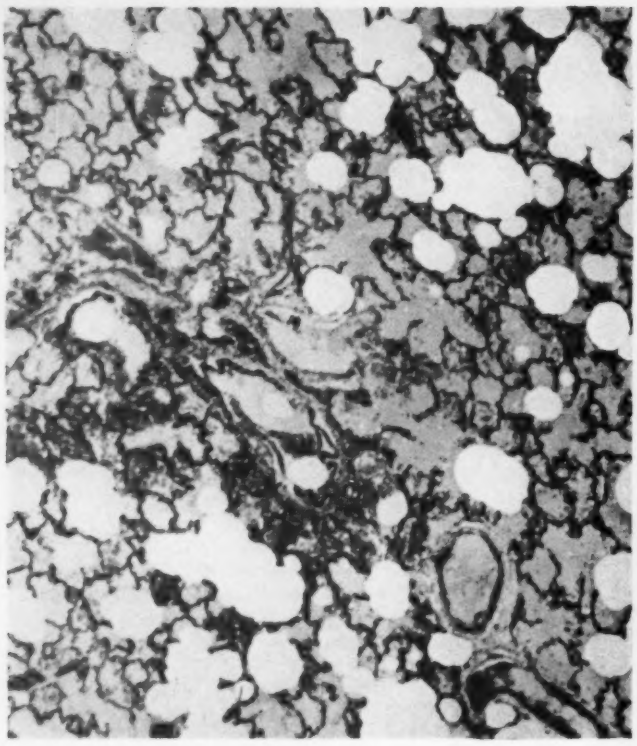


FIG. 1

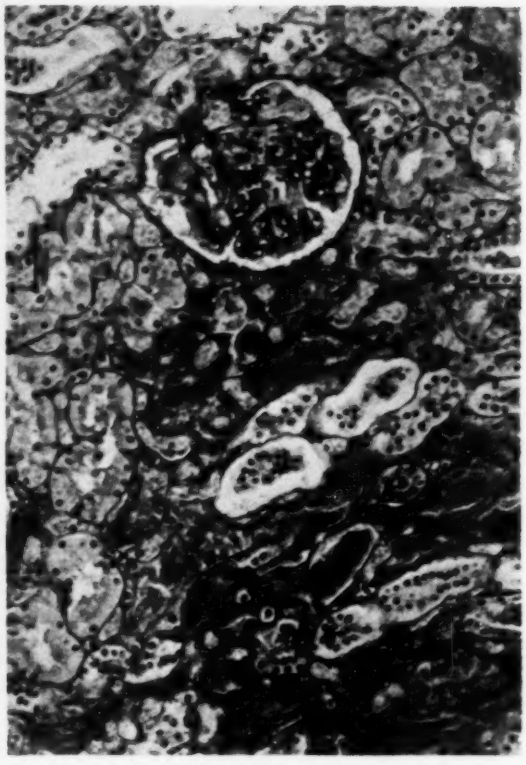


FIG. 3

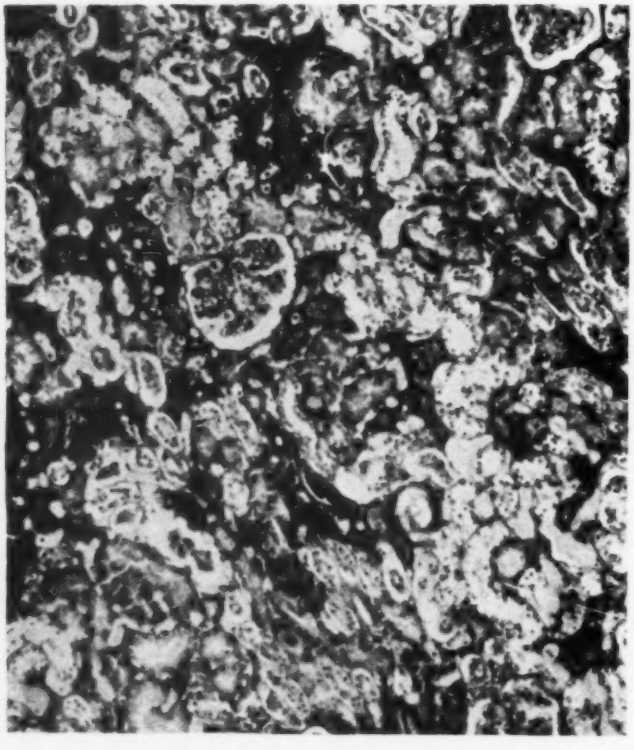


FIG. 2

FIG. 1.—In this section of lung of Case 1 there is massive pulmonary oedema, the fluid showing intense staining reaction. There is marked hyperaemia of the alveolar capillaries, some of which are tortuous and ruptured, with haemorrhages into some of the alveoli. Areas of emphysema are present. (Acid picro-Mallory x 92.)

FIG. 2.—In this section of renal cortex of Case 1 most of the glomeruli are normal, but the proximal convoluted tubules show complete necrosis and contain condensed granular material. The darkly staining necrotic tubules contrast sharply with the unaffected tubules. (Acid picro-Mallory x 80.)

FIG. 3.—Another section of renal cortex of Case 1 at higher magnification showing in greater detail the necrosis of the convoluted tubules with their content of condensed granular material. (Acid picro-Mallory x 130.)

normally collapsed, and only a few showed congestion, although some of these had blood in the glomerular spaces. In the tubules a striking lesion was observed (Figs. 2 and 3). A complete coagulative necrosis of the epithelium was present in many of the first convoluted tubules, in rather fewer of the second convoluted tubules, and in the loops of Henle, particularly the ascending limb. Many of the collecting tubules contained ribbon-like casts of condensed granular material, but no blood pigment was observed and the epithelium was intact.

Discussion

The minimum lethal dose for man of a gaseous poison can seldom be learned from accidental poisoning. On the other hand, when a group of people is involved the variation in susceptibility is often shown to be curiously wide (Duvoir, Fabre, and Layani, 1937 ; Michaux, Clercy, and Lechevallier, 1945 ; Michaex, Courchet, and Lechevallier, 1944 ; Johnstone, 1945). As far as can be ascertained the cabin door had been open before Cases 1 and 2 left to return to the school, but when the searchers arrived this door was locked and they had to force their way in. Presumably the survivor of this group (Case 3) had been exposed to the same concentration of vapour as the remainder of the party.

The delayed action of methyl bromide, similar to that of phosgene, is already known, but it is noteworthy that one boy walked three and a half miles without feeling more than vaguely ill (Case 1), then collapsed and was dead within 15 hours.

It appears that after the period of silent absorption the clinical picture depends on a threefold effect : damage to the respiratory system fairly localized to its periphery, and, like phosgene, mainly affecting the capillaries ; rapid damage to the renal tubular epithelium produced either by a toxic effect of the methyl bromide (or breakdown product) or by ischaemia through its action on the renal capillaries ; and thirdly a cerebral upset which, in view of the timing, can hardly be secondary to either the pulmonary or the renal upset.

In the kidneys the appearances certainly suggest a selective toxic action on the tubules, with results very similar to those described by Bywaters and Dible (1942) in " crush syndrome ", although the tubular casts do not give the pink hyaline staining mentioned by these authors. This tubular damage also resembles closely the renal changes seen after excessive vomiting (McLetchie, 1943) and carbon tetrachloride poisoning (Woods, 1946 ; Moon, 1956). The tubulo-venous communications, originally discovered by Dunn, Gillespie, and Niven (1941) in the " crush syndrome " and since reported in the kidney after excessive vomiting and after carbon tetrachloride poisoning, were not found in our cases. It may well be that these differences are related to the time of survival. It is of course scarcely possible to say when exactly the kidney of the " crush syndrome " received its toxic dose, but the shortest case described by Bywaters and Dible (1942) survived for four days after the onset of renal symptoms. McLetchie's case survived 16 days, as did that of Woods, whereas our cases were dead within 18 hours of exposure.

The distribution of the tubular necrosis is so sharply confined to the region where changes in reaction and concentration normally occur (Dunn and others, 1941) that one might reasonably postulate a local breakdown of the methyl bromide with the formation of toxic substance. On the other hand a vascular upset could be the basis of the damage, and it may be recalled that as long ago as 1915 Oliver suggested such a mechanism in corrosive sublimate poisoning. His hypothesis was that the mercuric chloride brought about an intense vascular stasis in the kidney and an ischaemic necrosis of the tubules resulted. This latter part of his idea received some confirmation in the recent finding by Wainwright (1950) that a similar tubular necrosis follows temporary experimental occlusion of the renal artery. It seems fairly certain that in the lungs methyl bromide produces its main damaging effect on the blood vessels, and the possibility of its doing likewise in the kidneys cannot be lightly dismissed.

The anuria could be explained on the basis either of a leakage of glomerular filtrate back across the damaged tubules (Dunn and others, 1941) or of the intense stasis, although this latter seems less probable as so many of the glomeruli were apparently normal.

The development of uraemia after inhalation of methyl bromide has been described by Benatt and Courtney (1948), but there were no convulsions and recovery followed. In our cases the convulsions appeared before a true uraemia could possibly have developed, and it is reasonable to assume that their occurrence points to a direct effect on the brain as a result of greater dosage.

The late appearance of optic disturbance raised the possibility that the methyl bromide was being split in the body with the formation of methyl alcohol, but, as the survivors do not suffer from any detectable impairment of vision, it is unlikely that methyl alcohol was concerned either here or in the production of the other nervous symptoms.

Summary

The results of poisoning by the inhalation of methyl bromide are described in an incident in

which eight boys were exposed to the vapour, six of whom died. The main clinical features and post-mortem findings are given, and a note on the survivors two years after the accident.

We wish to thank Dr. J. Morgan and Dr. J. Gordon Clark for the clinical details, Dr. G. R. Tudhope, Dr. W. Fyffe Dorward, and Dr. A. Inglis for the use of post-mortem material, and Professor A. C. Lendrum for his help throughout the study.

REFERENCES

Bywaters, E. G. L., and Dible, J. H. (1942). *J. Path. Bact.*, **54**, 111.
Benatt, A. J., and Courtney, T. R. B. (1948). *British Journal of Industrial Medicine*, **5**, 21.
Dunn, J. S., Gillespie, M., and Niven, J. S. F. (1941). *Lancet*, **2**, 549.
Duvoir, M., Fabre, R., and Layani, F. (1937). *Bull. Soc. méd. Hôp. Paris*, **53**, 1540.
Gray, P. H. K. (1944). *J. roy. nav. med. Serv.*, **30**, 214.
Holling, H. E., and Clarke, C. A. (1944). *Ibid.*, **30**, 218.
Johnstone, R. T. (1945). *Industr. Med.*, **14**, 495.
McLetchie, N. G. B. (1943). *J. Path. Bact.*, **55**, 17.
Mazel, P., Bourret, J., and Roche, L. (1946). *Arch. Mal. prof.*, **7**, 38.
Michaux, J., Clercy, A., and Lechevallier, J. (1945). *Ibid.*, **6**, 143.
——, Courchet, A., and Lechevallier, J. (1944). *Rev. Neurol.*, **76**, 229.
Moon, H. D. (1950). *Amer. J. Path.*, **26**, 1041.
Oliver, J. (1915). *J. exp. Med.*, **21**, 425.
Oettingen, W. F. von (1946). *Publ. Hlth Bull., Wash.*, No. 185.
Ramond, L., and Lacorne, J. (1942). *Bull. Soc. méd. Hôp. Paris*, **58**, 158.
Schuler (1839). *Dtsch. Vjschr. öff. GesundhPfl.*, **31**, 696. Quoted by von Oettingen.
Wainwright, J. (1950). *Brit. J. exp. Path.*, **31**, 400.
Woods, W. W. (1946). *J. Path. Bact.*, **58**, 767.

APPENDIX

TABLE 1

LABORATORY FINDINGS IN CASE 2

Date	Blood Urea (mg./100 ml.)	Blood Chloride (as NaCl) (mg./100 ml.)	Total Serum Proteins (g./100 ml.)	Serum Albumin (g./100 ml.)	Alkaline Phosphatase (K. and A. units/100 ml.)	Urine
November 5, 1947 ..	65	456	6	3·9	30	Nil
,, 6, ,, ..	100	364	5·8	4·1	20	Nil
,, 7, ,, ..	119	351	5·8	4·1	20	Albumin ++++ Granular casts
,, 8, ,, ..	190	424	6	4	20	Albumin +++ Granular casts
,, 9, ,, ..	200	468	6	4	16	Albumin ++ Few casts
,, 10, ,, ..	224	448	—	—	—	Albumin Epithelial casts
,, 11, ,, ..	195	—	—	—	12	—
,, 13, ,, ..	190	—	—	—	7	—
Urea clearance.. ..	15·7*	—	—	—	—	—
November 15, 1947 ..	147	—	7	4·8	—	—
Urea clearance.. ..	13·1	—	—	—	—	—
November 20, 1947 ..	110	—	—	—	—	—
Urea clearance.. ..	29·8	—	—	—	—	—
November 27, 1947 ..	31	468	7	4·8	7	Urine clear
Urea clearance.. ..	65	—	—	—	—	—
December 4, 1947 ..	30	468	7·1	4·8	7	—
Urea clearance.. ..	50·5	—	—	—	—	—

* Van Slyke urea clearance is expressed as a percentage of average normal function

TABLE 2

LABORATORY FINDINGS IN CASE 3

Date	Blood Urea (mg./100 ml.)	Blood Chloride as NaCl (mg./100 ml.)	Total Serum Protein (g./100 ml.)	Serum Albumin (g./100 ml.)	Alkaline Phosphatase (K. and A. Units/100 ml.)	Urine
November 5, 1947 ..	86	—	—	—	—	Nil
,, 6, ,, ..	110	361	6·5	4·4	8	Nil
,, 7, ,, ..	85	302	—	—	—	Albumin +++ Granular casts ++++ Epithelial casts Few pus cells
,, 8, ,, ..	75	402	6·5	4·2	—	—
,, 9, ,, ..	54	440	6·4	4·1	8	Albumin +
,, 10, ,, ..	48	468	6	4	—	Few granular casts Albumin + Few hyaline casts
,, 11, ,, ..	32	448	—	—	—	—
,, 13, ,, ..	33	—	—	—	—	Urine clear
Urea clearance.. ..	70·7*	—	—	—	—	—
November 18, 1947 ..	28	429	6	4	7	—
Urea clearance.. ..	62	—	—	—	—	—
December 3, 1947, as an out-patient	32	487	7	4·6	6	—

* Van Slyke urea clearance is expressed as a percentage of average normal function

Note. Blood bromide estimations were not made.

The laboratory findings in Case 1 were as follows :—
Whole blood chlorides (as NaCl) .. 370 mg. per 100 ml.
Blood urea .. 95 mg. per 100 ml.
Plasma alkaline phosphatase .. 39 units per 100 ml. (King-Armstrong units).

Brit. J. industr. Med., 1952, **9**, 50.

VANADIUM POISONING FROM CLEANING OIL-FIRED BOILERS

BY

N. WILLIAMS

From the London Transport Executive

(RECEIVED FOR PUBLICATION MAY 1, 1951)

The vanadium content of crude oil ash varies considerably according to its source. It may be as high as 45% in Venezuelian and 14% in Iranian crude oil or as low as a trace in Wyoming crude oil and none in the Pennsylvanian product (Dunstan, 1938). As fuel oils are residual oils left after the distillation of the more volatile hydrocarbons, they will contain a higher proportion of vanadium than the corresponding crude oils. Thus an oil with an ash content of 0·1% containing 40% of vanadium as V_2O_5 would produce 1 lb. of vanadium pentoxide for 11 tons of oil burnt. A significant proportion of the vanadium accumulates in the gas passages of boilers. This paper describes the symptoms and clinical findings in men cleaning oil-fired boilers, and sets out evidence that vanadium was responsible.

After the recent war a generating station was partly converted to burning fuel oil owing to shortage of coal. After cleaning the oil-fired boilers the men noticed symptoms which they associated with the work. Before this conversion there had been no complaints from the boiler-cleaners of any harmful effect on their health.

The boilers are probably the largest oil-fired land installations in this country, each boiler consuming about 150 tons of fuel oil per week. The lower part of the boiler, into which is sprayed the atomized oil, is known as the combustion chamber, which is lined by refractory fire-bricks, and on its rear and side walls are the vertical generating tubes. In the upper part of the boiler are more generating tubes interspersed between which are the superheater tubes. Considerable quantities of petroleum soot are deposited in both the combustion and superheater chambers.

Each boiler requires cleaning once a year in order to maintain its efficiency, and it has been found necessary at these times to renew the fire-brick lining. It takes a gang of eight men about five days to clean a boiler, after which the bricklayers enter to dismantle the fire-brick walls and build new ones.

The boiler cleaning methods in use when the investigation began produced large quantities of dust. The combustion chamber was cleaned by brushing the soot off the walls, and the boiler tubes by tapping with a rod, the soot falling off as a result of the vibration. In the superheater chamber the banks of tubes had to be cleaned by a compressed air jet from a nozzle, as it was difficult to reach them by other means (Fig. 1). Dismantling the fire-brick walls also produced dust, and the bricklayers complained of similar, though less severe, symptoms than those described by the boiler-cleaners (Fig. 2). The scaffolders, who are the first to enter the boiler in order to erect the platforms from which the cleaners work, have had symptoms similar to those of the bricklayers, but the cases reported in this paper are all boiler-cleaners.

Methods of Analysis

The vanadium content of the urine samples was determined by a colorimetric method described by Sandell (1950) in which sodium tungstate is used. The method was checked by estimating vanadium in the urines of men not exposed to petroleum soot, none being detected in these samples, and urines to which known quantities of ammonium metavanadate were added. It was found that the method was accurate in determining quantities as low as 0·02 mg. per specimen. Samples of dust were collected from different parts of the boilers during cleaning operations. Measured volumes of dust-laden air were drawn through distilled water contained in an aspirator packed with Lessing rings, a guard aspirator also being fitted as a precaution. Three separate samples of 3·7, 4·5, and 6·8 cu. m. were collected, the air being passed at about 7·1 cu.

FIG. 1.—Boiler-cleaners demonstrating methods of dislodging soot from generator and superheater tubes. The one on the left is using a compressed air lance, and on the right the cleaner is tapping the tubes with a rod.

FIG. 1

FIG. 2.—Bricklayers dismantling a fire-brick wall. The man on the right is spraying the bricks with water.

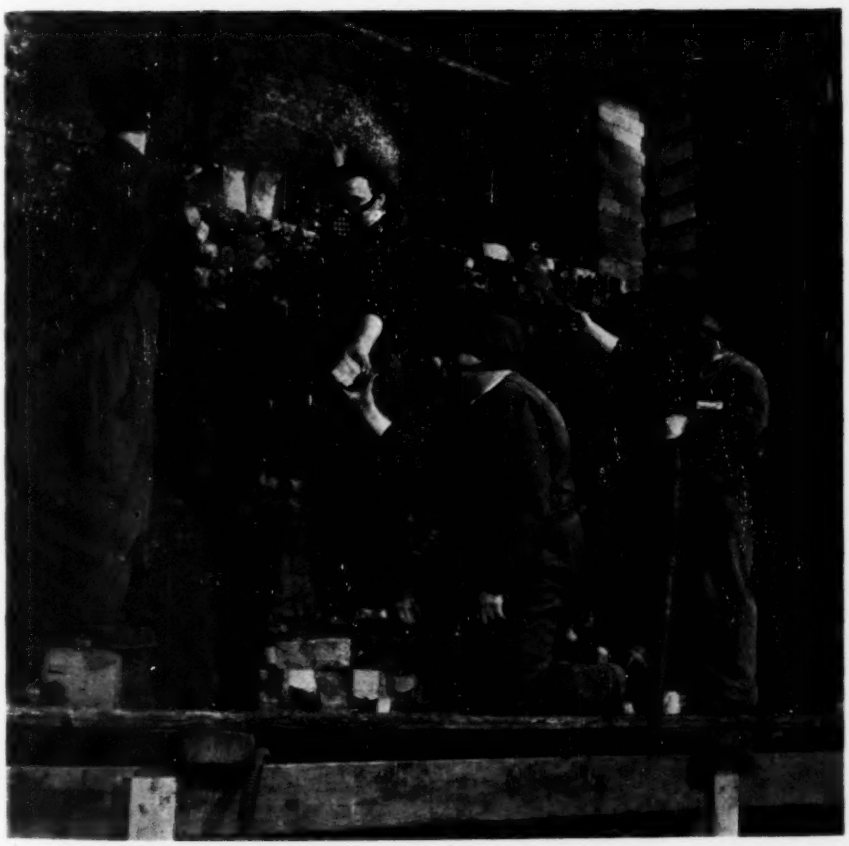


FIG. 2

m. per hour. Vanadium was estimated both in the resultant solution and suspended solids. Thermal precipitator samples were used to estimate particle size and concentration. The microscope technique involved the use of both 4 mm. and 2 mm. objectives. Particles counted ranged from 11 to 0·44 microns with the 4 mm. objective, and 4 to 0·15 microns using the 2 mm. objective.

Symptomatology

Boiler-Cleaners' Complaints.—All the eight men engaged on this work complained of symptoms associated with cleaning oil-fired boilers. The first symptoms usually occurred between half and one hour after starting work, but in some cases were delayed for 12 hours. They consisted of rhinorrhoea, sneezing, watering of the eyes, soreness of the throat and behind the sternum. This group of symptoms can be described as the primary symptoms, the secondary ones appearing after a period of six to 24 hours. They were dry cough, wheezing, severe dyspnoea causing the man to rest after climbing a 20-foot ladder, lassitude, and depression with a disinclination to follow the usual evening activities. A greenish-black coating developed on the tongue which faded two or three days after contact with petroleum soot was over. Some of the men noted that the cough became paroxysmal and productive.

These symptoms continued while at work and only became less severe three days after ceasing work. In one man the wheezing and dyspnoea persisted for over a week, but none noticed any permanent ill-effects.

Personal Observations.—I entered one of the oil-fired boilers while it was being cleaned and remained there for about one hour to obtain first-hand experience of the symptoms. Rhinorrhoea, sneezing, and watering of the eyes occurred within 15 minutes. Three hours later the secondary symptoms began to develop : dry cough, wheezing, dyspnoea, and soreness behind the sternum. Cough and wheezing continued throughout the night disturbing sleep. During the next day dyspnoea became more intense, it being impossible to walk at even a moderately brisk pace on the level. Climbing 30 stairs necessitated a short period of rest before continuing. There was a general feeling of depression, and it was difficult to take the usual interest in work. Cough became productive after the second day. The bronchospasm was not relieved by "benadryl" but ephedrine and stramonium gave some relief. The dyspnoea had disappeared by the end of one week, but the cough persisted for a further week. It had at one time been suggested that the symptoms were due to sulphur dioxide, but the absence of the characteristic smell and the delay in the onset of the symptoms excluded this possibility.

Clinical Reports

All eight boiler-cleaners were examined before and after work, that is after exposures lasting approximately one week. It was obvious from a knowledge of the men's previous personalities that they were in low spirits, looked tired, listless, and pale. One man complained that coughing had been sufficiently severe to produce vomiting. Another noticed that the tips of his cigarettes turned green.

Examination of the tongue revealed a coating on the dorsum varying from greenish-black to greenish-yellow. It was not possible to remove the discoloration by scraping. In two of the men there were signs of generalized bronchospasm and bronchitis. Two other men had developed râles in the right axillary region. Cardiac examination revealed no abnormality. In two men slight tremor of the hands developed.

X-ray films of the chest, electrocardiograms, and routine examination of the urine for albumin, sugar, and blood revealed no abnormality.

Case Reports

Case 1.—This man, aged 38, had been a boiler-cleaner from 1947 to 1949. He was examined after five days' cleaning on an oil-fired boiler. He complained of sneezing within two hours of starting work and developed a cough the same evening. He was dyspnoeic the next day on ladder climbing, was depressed, and felt tired. He noticed that cigarette tips turned green. Examination revealed a greenish-black coating on the tongue, many high-pitched rhonchi throughout the chest, and râles in the right axillary region. Blood pressure was 110/70 (pre-exposure 138/65). A radiograph of the chest revealed no abnormality. Urine analysis showed 0·08 mg. vanadium in 210 ml. urine passed during the day and 0·02 mg. vanadium in an early morning specimen of 297 ml.

Case 2.—Aged 40, he had been a boiler-cleaner from 1946 to 1949. He was examined after two days' exposure. He developed rhinorrhoea and sneezing within three hours of starting work and a dry cough the same evening. He felt drowsy, and was dyspnoeic on climbing stairs. Examination revealed a yellowish-green coating on the tongue, scattered rhonchi over both lungs with râles at both bases. Blood pressure was 110/75 (pre-exposure 140/95). A radiograph of the chest was normal. No vanadium was detected in the urine.

Case 3.—This man, aged 32, had been a boiler-cleaner from 1947 to 1949. He was examined two days after ceasing two days' work in an oil-fired boiler. He developed rhinorrhoea and sneezing half an hour after starting work. He noticed tightness of the chest the same evening, and felt depressed. Next day dry cough began,

and he became dyspnoeic and orthopnoeic. He had to sit down after climbing a flight of stairs. Examination revealed a yellowish-green coating on the tongue. A fine tremor of the hands was evident. No physical signs were detected in the chest. Blood pressure was 120/82 (pre-exposure 145/90). A radiograph of the chest was normal. No vanadium was detected in the urine.

Case 4.—Aged 43, he had been a boiler-cleaner from 1946 to 1949. He was examined after five days' exposure. He developed rhinorrhoea and sneezing within half an hour of starting work and later soreness of the throat and chest. Dry cough started later the same day. Next day he became dyspnoeic and had to rest after climbing a ladder. He felt depressed. By the fifth day cough had become paroxysmal and induced vomiting. Examination revealed a pale green coating on the tongue. No physical signs were detected in the chest. Blood pressure was 105/70 (pre-exposure 128/80). A day sample of 230 ml. urine contained a trace of vanadium.

Case 5.—This man, aged 39, had been a charge hand boiler-cleaner from 1946 to 1949. He was examined after five days' exposure. No symptoms appeared on the first day, but rhinorrhoea and cough developed on the second day, with some wheezing and a tight feeling across the chest. Cough was productive on the third day. The patient was dyspnoeic on climbing stairs, and felt listless. Examination revealed that he was paler than normal; the tongue was light green posteriorly. No physical signs were detected in the chest. Blood pressure was 110/65 (pre-exposure 125/80). A radiograph of the chest was normal. No vanadium was detected in the urine.

Case 6.—The patient was aged 35 and had been a boiler-cleaner from 1948 to 1949. He was examined four days after ceasing boiler-cleaning, an operation lasting three days. He developed rhinorrhoea and cough towards the end of the first day, but had no wheezing. He lacked concentration. Cough ceased two days after exposure ended. Examination showed a pale yellow coating over the tongue and a few râles in the right axilla. Blood pressure was 110/70 (pre-exposure 150/80). A radiograph of the chest was normal. The urine, 152 ml., contained a trace of vanadium.

Case 7.—This man, aged 39, had been a boiler-cleaner from 1948 to 1949. He was examined after five days' exposure. He developed sneezing and rhinorrhoea within six hours of starting work. Cough began next day and soon became productive. He was dyspnoeic on climbing a ladder and had to rest at the top. Examination showed a greenish-black coating on the tongue, and a fine tremor of the hands. No physical signs were detected in the chest. Blood pressure was 150/90 (pre-exposure 150/90). A radiograph of the chest was normal. No vanadium was detected in the urine.

Case 8.—The last patient, aged 26, had been a boiler-cleaner from 1947 to 1949. He had had occasional cough cleaning coal-fired boilers. He was examined after five days' exposure. He developed rhinorrhoea, sore throat, and cough within one hour of starting work, and felt a tightness of the chest the same evening. He was dyspnoeic next day and had to rest after climbing a ladder. He noticed a bitter taste in the mouth, and felt depressed. Examination showed a thick, dark green coating on the tongue. No physical signs in the chest were detected. Blood pressure was 120/75 (pre-exposure 130/90). A radiograph of the chest was normal. No vanadium was detected in the urine.

Vanadium in Urine

Specimens over a period of 24 hours, on the last day of working at boiler cleaning, were collected from each man, precautions being taken to prevent contamination by dust from the clothes and hands.

The largest amounts of vanadium were detected in the urine samples from Case 1 (0·4 mg. and 0·07 mg. per litre). It is interesting to note that this man was regarded clinically as being the most severely affected.

Traces were found in the specimens of Cases 4 and 6, one of whom had severe symptoms and the other mild. Vanadium was not detected in the urine of the remaining cases.

Atmospheric Dust

Table 1 gives the average results obtained from two thermal precipitator samples taken in the superheater. On the average the numerical concentration of dust particles not exceeding 11 microns in diameter was 3,526 particles per 1 ml. of air, and of these 93·6% did not exceed 1 micron in size. Although there was such a numerical preponderance of fine particles these accounted for only a small proportion of the weight of dust in the air. The weight concentration of particles within different size ranges has been computed on the assumptions that the particles are spherical in shape, and that the dust has a specific gravity of 2. The results of these calculations are shown in the fourth column of Table 1, where it is seen that the mass concentration of dust below 1 micron in size was only 0·36 mg. per cu. m. In the last column of Table 1 the weight concentrations of particles of various sizes are shown as percentages of the total estimated weight concentration of particles not greater than 11 microns. It should be remembered, however, that the estimate of the total weight concentration (12·3 mg. per cu. m.) of particles of this range of size can give no indication of the weight concentration of the whole dust when there are present many particles greatly exceeding 11 microns in diameter. That is made clear by comparing the weight concentrations in Table 1 with those in Table 2 which gives the results of the three samples taken from boilers during cleaning operations, by aspirating air through distilled water (Table 2). The range of particle size of the vanadium dust is not known but

m. per hour. Vanadium was estimated both in the resultant solution and suspended solids. Thermal precipitator samples were used to estimate particle size and concentration. The microscope technique involved the use of both 4 mm. and 2 mm. objectives. Particles counted ranged from 11 to 0·44 microns with the 4 mm. objective, and 4 to 0·15 microns using the 2 mm. objective.

Symptomatology

Boiler-Cleaners' Complaints.—All the eight men engaged on this work complained of symptoms associated with cleaning oil-fired boilers. The first symptoms usually occurred between half and one hour after starting work, but in some cases were delayed for 12 hours. They consisted of rhinorrhoea, sneezing, watering of the eyes, soreness of the throat and behind the sternum. This group of symptoms can be described as the primary symptoms, the secondary ones appearing after a period of six to 24 hours. They were dry cough, wheezing, severe dyspnoea causing the man to rest after climbing a 20-foot ladder, lassitude, and depression with a disinclination to follow the usual evening activities. A greenish-black coating developed on the tongue which faded two or three days after contact with petroleum soot was over. Some of the men noted that the cough became paroxysmal and productive.

These symptoms continued while at work and only became less severe three days after ceasing work. In one man the wheezing and dyspnoea persisted for over a week, but none noticed any permanent ill-effects.

Personal Observations.—I entered one of the oil-fired boilers while it was being cleaned and remained there for about one hour to obtain first-hand experience of the symptoms. Rhinorrhoea, sneezing, and watering of the eyes occurred within 15 minutes. Three hours later the secondary symptoms began to develop : dry cough, wheezing, dyspnoea, and soreness behind the sternum. Cough and wheezing continued throughout the night disturbing sleep. During the next day dyspnoea became more intense, it being impossible to walk at even a moderately brisk pace on the level. Climbing 30 stairs necessitated a short period of rest before continuing. There was a general feeling of depression, and it was difficult to take the usual interest in work. Cough became productive after the second day. The bronchospasm was not relieved by " benadryl " but ephedrine and stramonium gave some relief. The dyspnoea had disappeared by the end of one week, but the cough persisted for a further week. It had at one time been suggested that the symptoms were due to sulphur dioxide, but the absence of the characteristic smell and the delay in the onset of the symptoms excluded this possibility.

Clinical Reports

All eight boiler-cleaners were examined before and after work, that is after exposures lasting approximately one week. It was obvious from a knowledge of the men's previous personalities that they were in low spirits, looked tired, listless, and pale. One man complained that coughing had been sufficiently severe to produce vomiting. Another noticed that the tips of his cigarettes turned green.

Examination of the tongue revealed a coating on the dorsum varying from greenish-black to greenish-yellow. It was not possible to remove the discoloration by scraping. In two of the men there were signs of generalized bronchospasm and bronchitis. Two other men had developed râles in the right axillary region. Cardiac examination revealed no abnormality. In two men slight tremor of the hands developed.

X-ray films of the chest, electrocardiograms, and routine examination of the urine for albumin, sugar, and blood revealed no abnormality.

Case Reports

Case 1.—This man, aged 38, had been a boiler-cleaner from 1947 to 1949. He was examined after five days' cleaning on an oil-fired boiler. He complained of sneezing within two hours of starting work and developed a cough the same evening. He was dyspnoeic the next day on ladder climbing, was depressed, and felt tired. He noticed that cigarette tips turned green. Examination revealed a greenish-black coating on the tongue, many high-pitched rhonchi throughout the chest, and râles in the right axillary region. Blood pressure was 110/70 (pre-exposure 138/65). A radiograph of the chest revealed no abnormality. Urine analysis showed 0·08 mg. vanadium in 210 ml. urine passed during the day and 0·02 mg. vanadium in an early morning specimen of 297 ml.

Case 2.—Aged 40, he had been a boiler-cleaner from 1946 to 1949. He was examined after two days' exposure. He developed rhinorrhoea and sneezing within three hours of starting work and a dry cough the same evening. He felt drowsy, and was dyspnoeic on climbing stairs. Examination revealed a yellowish-green coating on the tongue, scattered rhonchi over both lungs with râles at both bases. Blood pressure was 110/75 (pre-exposure 140/95). A radiograph of the chest was normal. No vanadium was detected in the urine.

Case 3.—This man, aged 32, had been a boiler-cleaner from 1947 to 1949. He was examined two days after ceasing two days' work in an oil-fired boiler. He developed rhinorrhoea and sneezing half an hour after starting work. He noticed tightness of the chest the same evening, and felt depressed. Next day dry cough began,

and he became dyspnoeic and orthopnoeic. He had to sit down after climbing a flight of stairs. Examination revealed a yellowish-green coating on the tongue. A fine tremor of the hands was evident. No physical signs were detected in the chest. Blood pressure was 120/82 (pre-exposure 145/90). A radiograph of the chest was normal. No vanadium was detected in the urine.

Case 4.—Aged 43, he had been a boiler-cleaner from 1946 to 1949. He was examined after five days' exposure. He developed rhinorrhoea and sneezing within half an hour of starting work and later soreness of the throat and chest. Dry cough started later the same day. Next day he became dyspnoeic and had to rest after climbing a ladder. He felt depressed. By the fifth day cough had become paroxysmal and induced vomiting. Examination revealed a pale green coating on the tongue. No physical signs were detected in the chest. Blood pressure was 105/70 (pre-exposure 128/80). A day sample of 230 ml. urine contained a trace of vanadium.

Case 5.—This man, aged 39, had been a charge hand boiler-cleaner from 1946 to 1949. He was examined after five days' exposure. No symptoms appeared on the first day, but rhinorrhoea and cough developed on the second day, with some wheezing and a tight feeling across the chest. Cough was productive on the third day. The patient was dyspnoeic on climbing stairs, and felt listless. Examination revealed that he was paler than normal; the tongue was light green posteriorly. No physical signs were detected in the chest. Blood pressure was 110/65 (pre-exposure 125/80). A radiograph of the chest was normal. No vanadium was detected in the urine.

Case 6.—The patient was aged 35 and had been a boiler-cleaner from 1948 to 1949. He was examined four days after ceasing boiler-cleaning, an operation lasting three days. He developed rhinorrhoea and cough towards the end of the first day, but had no wheezing. He lacked concentration. Cough ceased two days after exposure ended. Examination showed a pale yellow coating over the tongue and a few râles in the right axilla. Blood pressure was 110/70 (pre-exposure 150/80). A radiograph of the chest was normal. The urine, 152 ml., contained a trace of vanadium.

Case 7.—This man, aged 39, had been a boiler-cleaner from 1948 to 1949. He was examined after five days' exposure. He developed sneezing and rhinorrhoea within six hours of starting work. Cough began next day and soon became productive. He was dyspnoeic on climbing a ladder and had to rest at the top. Examination showed a greenish-black coating on the tongue, and a fine tremor of the hands. No physical signs were detected in the chest. Blood pressure was 150/90 (pre-exposure 150/90). A radiograph of the chest was normal. No vanadium was detected in the urine.

Case 8.—The last patient, aged 26, had been a boiler-cleaner from 1947 to 1949. He had had occasional cough cleaning coal-fired boilers. He was examined after five days' exposure. He developed rhinorrhoea, sore throat, and cough within one hour of starting work, and felt a tightness of the chest the same evening. He was dyspnoeic next day and had to rest after climbing a ladder. He noticed a bitter taste in the mouth, and felt depressed. Examination showed a thick, dark green coating on the tongue. No physical signs in the chest were detected. Blood pressure was 120/75 (pre-exposure 130/90). A radiograph of the chest was normal. No vanadium was detected in the urine.

Vanadium in Urine

Specimens over a period of 24 hours, on the last day of working at boiler cleaning, were collected from each man, precautions being taken to prevent contamination by dust from the clothes and hands.

The largest amounts of vanadium were detected in the urine samples from Case 1 (0·4 mg. and 0·07 mg. per litre). It is interesting to note that this man was regarded clinically as being the most severely affected.

Traces were found in the specimens of Cases 4 and 6, one of whom had severe symptoms and the other mild. Vanadium was not detected in the urine of the remaining cases.

Atmospheric Dust

Table 1 gives the average results obtained from two thermal precipitator samples taken in the superheater. On the average the numerical concentration of dust particles not exceeding 11 microns in diameter was 3,526 particles per 1 ml. of air, and of these 93·6% did not exceed 1 micron in size. Although there was such a numerical preponderance of fine particles these accounted for only a small proportion of the weight of dust in the air. The weight concentration of particles within different size ranges has been computed on the assumptions that the particles are spherical in shape, and that the dust has a specific gravity of 2. The results of these calculations are shown in the fourth column of Table 1, where it is seen that the mass concentration of dust below 1 micron in size was only 0·36 mg. per cu. m. In the last column of Table 1 the weight concentrations of particles of various sizes are shown as percentages of the total estimated weight concentration of particles not greater than 11 microns. It should be remembered, however, that the estimate of the total weight concentration (12·3 mg. per cu. m.) of particles of this range of size can give no indication of the weight concentration of the whole dust when there are present many particles greatly exceeding 11 microns in diameter. That is made clear by comparing the weight concentrations in Table 1 with those in Table 2 which gives the results of the three samples taken from boilers during cleaning operations, by aspirating air through distilled water (Table 2). The range of particle size of the vanadium dust is not known but

TABLE 1

THERMAL PRECIPITATOR SAMPLES TAKEN FROM SUPERHEATER DURING CLEANING OPERATION

Diameter of Particles (μ)	Number of Particles (per 1 ml. air)	Numerical Concentration of Particles (%)	Weight Concentration of Particles (mg. per cu. m.)	Weight Concentration of Particles (%)
0·15–1·0	3,300	93·6	0·36	2·9
1·0–5·5	217	6·14	4·09	33·3
5·5–11	9	0·26	7·85	63·8

TABLE 2

ANALYSIS OF DUST FROM BOILER DURING CLEANING

Sampling Point	Dust (mg./cu. m. air)	Vanadium (as % of dust)	Vanadium (mg./cu. m. air)
Superheater chamber	659	6·1	40·2
Superheater chamber	239	7·2	17·2
Combustion chamber	489	12·7	58·6

when advising on the use of suitable respirators it is safer to assume that the smallest dust particles contain vanadium.

Preventive Measures

Efforts were made to prevent or reduce the amount of the dust produced, but the main problem was to prevent the inhalation of the dust by the boiler-cleaners.

It was found that a large part of the boiler could be cleaned by an operator standing outside the boiler at the manhole using a lance several feet long, from which a jet of compressed air boosted to a very high pressure was ejected. The soot was drawn away from the operator and up the flue to the outside atmosphere by the induced draught fan. As certain parts of the boiler could not be reached by this method, men wearing dust respirators (Mark IV, Siebe Gorman), a type approved for use where there is a silicosis hazard, entered the boiler itself in order to complete the cleaning. When the induced draught fan could be used to advantage this was switched on.

Much soot dust was produced when the fire-brick walls were dismantled and a water spray was therefore used on the bricks as they were being dislodged. A tarpaulin was stretched over the top of the combustion chamber to prevent soot particles, dislodged from the boiler tubes by vibration, falling from the superheater chamber into the combustion chamber where men were working.

Two boilers have been cleaned using these methods without a single complaint of symptoms from the boiler-cleaners, scaffolders, or bricklayers.

More recently, two boiler-makers and two bricklayers have been engaged on repairs in a boiler which had not been previously cleaned. They wore their respirators only when it appeared to them that there was dust in the atmosphere and it is not surprising that they developed minor symptoms of vanadium intoxication. The vibration of the repair work must have caused a small amount of soot to get into the air of the combustion chamber. It has therefore been recommended that all men entering boilers which have not previously been completely cleaned should wear suitable respirators.

Discussion

A search of the literature has failed to disclose any reference to symptoms caused by this type of work, although it has been known for many years that petroleum and petroleum soot contained vanadium in varying proportions. Respiratory symptoms of vanadium poisoning among workers extracting vanadium from petroleum soot, obtained from the boilers of oil-fired liners, were described by Wyers (1946). Information obtained from a boiler-cleaning company revealed that they have paid increased wages since 1924 for men cleaning oil-fired boilers. The reasons for this have been obscured by time, but it would appear that there were two possible reasons: the dirtier nature of the petroleum soot and the unpleasant respiratory symptoms experienced. The management stated that the men still complained of a wheezing of the chest, but medical advice on this, as an industrial problem, had never been sought. They had, however, provided the men with a light mask with a cotton wool filter.

Sjöberg (1949) recorded four cases of bronchopneumonia, one of lobar pneumonia, and one of pleurisy among workers exposed to vanadium dust. The sick records of the boiler-cleaners over the last two years were examined, but they revealed no significant increase in sickness absence from any cause. This would appear to be in accordance with the views of Symanski (1939) who, in a very full account of vanadium poisoning, concluded that the work should be intermittent in order to allow recovery from adverse effects. In the present series of cases the system of working had, in fact, produced these conditions as the men work on oil-fired boilers for only about two weeks in every three months.

The blood pressure of the boiler-cleaners taken after exposure were in no case higher than the pre-exposure readings as might have been expected from the experience of Wyers (1946). In fact they were lower. No explanation is offered for these findings but possibly the men had become accustomed to medical examination by the time the later readings were taken.

Dutton (1911) described vanadium poisoning with symptoms and signs referable to disorders of the gastro-intestinal and renal systems. These were anorexia, nausea, and vomiting, and albumin, blood, and casts in the urine. He also observed anaemia, with a reduction both in the number of cells and of haemoglobin. No cases in the present series had symptoms or signs referable to these systems, though one man did develop a degree of pallor. Symanski (1939) also failed to observe any of these changes. However, two of the boiler-cleaners developed a fine tremor of the hands, a sign which Dutton and subsequent writers have observed.

In view of the risks of vanadium intoxication involved in cleaning oil-fired boilers, it is suggested that methods of cleaning these boilers should be reviewed and means devised which do not involve exposure to the harmful effects of the petroleum soot. Even intermittent exposures may lead to bronchitis or pneumonia. Men working on these boilers should be under medical supervision. It is probable that much respiratory disease occurs among boiler-cleaners, the true cause of which is not recognized. Finally, it is hoped that this paper may be of some value in drawing attention to the existence of the hazard.

Summary

Vanadium intoxication in eight men cleaning oil-fired boilers is described.

The method of investigation of the original complaint, the preventive measures instituted, and the results achieved are discussed.

It is suggested that methods of cleaning oil-fired boilers should be reviewed, and that men working on these boilers should be medically supervisied.

I am indebted to Mr. A. T. Wilford, the late superintendent of laboratories, and to Mr. H. E. Styles, present superintendent of laboratories, and their staff for the analyses of the dust and urine; to Mr. H. Branton, Generating Station Superintendent, for his help and cooperation; and to Dr. L. G. Norman, the Chief Medical Officer, for his advice in the preparation of this paper. The thermal precipitator estimations were carried out by the Fuel Research Station, Department of Scientific and Industrial Research.

References

Dunstan, A. E. (1938). "The Science of Petroleum," vol. 2, p. 1053. London.
Dutton, W. F. (1911). *J. Amer. med. Ass.*, **56**, 1648.
Sandell, E. B. (1950). "Colorimetric Determination of Traces of Metals," 2nd ed. (Chemical Analysis, vol. 3.) London.
Sjöberg, S. G. (1949). *Nord. Med.*, **41**, 500.
Symanski, H. (1939). *Arch. Gewerbepath. Gewerbehyg.*, **9**, 295.
Wyers, H. (1946). *British Journal of Industrial Medicine*, **3**, 177.

Brit. J. industr. Med., 1952, **9**, 56.

SALT LOSSES OF MEN WORKING IN HOT ENVIRONMENTS

BY

J. S. WEINER and R. E. van HEYNINGEN

From the Medical Research Council Climate and Working Efficiency Research Unit, Oxford

(RECEIVED FOR PUBLICATION OCTOBER 31, 1951)

The necessity for an adequate salt intake for people working in hot climates has been recognized for a long time (Moss, 1923). Salt deficiency is with some certainty known to cause heat cramps (Talbott, 1935; McCance, 1936; Ladell, 1949) and is very likely the cause of lesser degrees of ill-health and inefficiency (Taylor, Henschel, Mickelsen, and Keys, 1943; Ladell, Waterlow, and Hudson, 1944). To understand how such ill-effects arise, it is obviously necessary to establish the changes in salt metabolism associated with sweating at high temperatures. In reviews of this matter Ladell (1945) and Robinson (1949) have pointed to the confusion in the literature regarding the exact effects of dietary chloride and acclimatization on the chloride content of the sweat. The recent experiments of Conn and Johnston (1944; Conn, Johnston, and Louis, 1946) have thrown much light on this problem. This work indicates that when the salt loss during exposure to heat is greater than the dietary supply, the "negative" balance may only be temporary; a restriction in both sweat and urine chloride output takes place so that after some days the salt deficit is made good and the total salt output is readjusted to the level of intake. Conn's work is important in showing that balance is possible at levels of salt intake even as low as 6 g. per day for men sweating 5–6 kg. a day. Unfortunately, this, as well as earlier work, may give the impression that this restriction in salt loss is necessarily or invariably a part of the process of acclimatization to heat, whereas in logical extension of Conn's findings one would expect no decrease in sweat chloride on a sufficiently high salt intake. The sweat chloride content on higher salt diets during the acclimatization period seems not as yet to have been investigated in experiments like those of Conn in which the subjects lived continuously in the heat. In the earlier work of Black, McCance, and Young (1944), however, in which recumbent individuals were exposed daily for short periods in a radiant heat bath, a decrease in sweat chloride output did not, in fact, occur on a high salt diet whereas on a low level of intake a decrease took place.

The experiments reported in this paper are similar to those of McCance (1936) and Black, McCance, and Young (1944), in that they involve short periods of exposure to heat. They were carried out on working subjects exposed to strictly standardized conditions of work. When this investigation was nearly completed, papers by Robinson, Kincaid, and Rhamy (1950) appeared in which they reported results with which those of the present experiments are in substantial accord. It seems useful to record our results, for in addition to confirmation of an important physiological response to hot climates, they are concerned also with another aspect of this problem. In our experiments chloride analysis was made not only of the body sweat from the general body surface but also on sweat collected in arm bags. The difference in the composition between the sweat from these two collections helps to explain some of the confusion referred to by Robinson (1949) and Ladell (1945). Finally, a separate series of experiments on unacclimatized persons is presented because of its bearing on the "salt conserving" responses of the body at high temperatures.

Methods

Two series of experiments are reported, the first on subjects during acclimatization to heat, the second on unacclimatized subjects. Certain subsidiary experiments are referred to in the text.

Sweat Composition in Relation to Dietary Chloride During Acclimatization.—The five subjects, C, D, N, Br, and Ba were acclimatized to heat by working nude in the hot room for two hours on five or six days a week for two or three weeks. All except Br performed four

30-minute cycles, each of 20 minutes' work (step climbing, 1 ft. high, 12 times a minute), followed by 10 minutes rest; Br completed only three cycles. The five subjects were exposed to dry bulb 46·1° C., wet bulb 29·4° C., relative humidity 30%, air movement 50 ft./min. The subjects (except Ba) ate their normal diet with the addition of 10 g. of NaCl (171 mEq./chloride) after each hot room exposure.

The experiment on subject Ba was carried out in three stages. The first stage occupied seven days (Sunday to Saturday inclusive) when Ba ate his normal diet supplemented by 8 g. NaCl (137 mEq./chloride) daily and spent two hours in the hot room every day except Sunday. The second stage took six days (Sunday to Friday inclusive) when he took a diet deficient in salt, containing about 16 mEq./chloride a day (less than 1 g. NaCl). He was in the hot room on five days, Monday to Friday inclusive. For the third stage, the next four days (Saturday to Tuesday inclusive), he resumed his normal diet supplemented by 8 g. NaCl (137 mEq./chloride) daily. He worked in the hot room on Monday and Tuesday.

Urine collections (24-hourly) were made daily, starting each morning from the time when the subject entered the hot room. They were analysed for chloride. Faecal loss of chloride and that lost in the sweat when the subject was not in the hot room were neglected.

Partition of Chloride between Sweat and Urine in Unacclimatized Subjects.—Two subjects (Mol and Mac) each worked for two hours (i.e., four cycles) in eight different environments covering a range of temperature from 37·2° C. to 44·4° C. at 40% room heat, and from 27·7° C. to 33·3° C. at approximately 100% room heat. To keep the subjects unacclimatized to heat as far as possible they were exposed only three times a fortnight. Each subject ate 5 g. salt (86 mEq.) after each exposure. On the days on which the subject was in the hot room 24-hour collections of urine were made from the time he entered the hot room until the same time next day; the collection made while he was actually in the hot room was kept separate from the rest; both were analysed for chloride. The total sweat output was also analysed for chloride. Twenty-four-hour urine collections were made on the days preceding those in the hot room, thus giving an estimate of the total normal output (and therefore an indication of the intake) of chloride. It was not feasible to control the diet of these subjects. On the day after an exposure (as soon as the 24-hour urine collection had been completed) the subject took salt by mouth to compensate for that lost in the sweat.

Sweat Composition.—Before each experiment the subjects had a shower and were washed with a jet of distilled water. Arm sweat was collected in a dry oilskin irrigation envelope which had completely but loosely encased the whole of one arm and hand and fitted firmly around the top of the arm just below the axilla. The arm was well washed with distilled water and dried before the bag was put on. Sweat was drained through an outlet at the bottom of the bag every half hour. The sweat from the rest of the body surface was collected in a large bath in which the subject spent the whole of the time he was in the hot room. The sides of the bath came up to his shoulders so that no sweat splashed outside. There was a slope towards one end so that the sweat and subsequent washings of body and bath could be drained into a weighed bucket.

At the end of the experiment the room was cooled down rapidly to prevent further sweating. The arm bag was removed and the arm washed with distilled water until the washings were chloride-free. The combined washings and the serial arm collections were analysed for chloride. The volume of sweat adhering to the arm before the final washing was taken to be xy/z where x is the volume of diluted sweat after it was washed down, y the chloride concentration of this diluted sweat, and z the concentration of the last collection. It is assumed that the concentration of the final adherent sweat is the same as that in the last collection.

The rest of the body surface was washed down with distilled water, and the subject then left the bath and was weighed. The sides of the bath were washed down with distilled water until the washings were chloride-free, and the sweat and washings from the body (about 5 l.) collected in the bucket which was then re-weighed. The subject was then dried by rubbing down with absorbent (salt-free) paper which was then put in with the washings in the bucket. The subject was then re-weighed. The chloride concentration of the diluted sweat was determined. The corresponding value for undiluted sweat was calculated by multiplying the values by the factor $\left[\frac{\text{weight of diluted sweat}}{\text{total sweat loss (less arm bag sweat)}}\right]$. From the serial sweat collections and the final arm washing the total output and average composition of arm bag sweat over the whole sweating period was also calculated.

The actual length of time over which sweat was collected did not differ by more than a few minutes from day to day (125 minutes for the four-cycle experiments and 95 minutes for the three-cycle experiments). After the concentrations had been calculated, the volumes of the arm and body sweat were corrected to be equivalent to the same length of time each day (125 minutes or 95 minutes).

Sweat Loss.—Sweat loss was calculated from the loss in weight, allowing for water drunk, urine passed, and respiratory loss of water. It was necessary to apply this last correction in these experiments because of the low rate of sweating at the lower environmental temperatures. The correction, calculated from the ventilation rate of the subject and the relative humidity of the surroundings, varied from 14 to 70 g. over the two-hour exposure; it accounted for about 25% of the uncorrected sweat loss at the lowest ambient temperatures and about 2% at the highest ambient temperatures.

Skin Temperatures.—In subjects N and Ba skin temperatures were measured on 11 spots of the body, and on the upper arm, forearm, and wrist within the bag. The 11 spots on the body were: forehead, wrist, forearm, upper arm, chest, scapula, kidney, outer

surface of the thigh, medial surface of the thigh, calf, and toe. The measurements, which were taken just before the man started and at the end of each spell of work, were made by means of a 40 gauge copper constantan thermocouple mounted on a small plastic holder and they were recorded by a potentiometer and a Tinsley 2-second galvanometer. The average surface temperature was obtained from the 11 skin temperatures by weighting according to the proportion of the surface area represented by each thermocouple (Belding, Darling, Griffin, Robinson, and Turrell, 1945). An average of the three values on each arm (upper, forearm, hand) was also calculated. The five values for the body skin temperatures thus obtained for each experiment (initial and after the four work periods) were averaged to give the average body skin temperature of the experiment. In this average rather too much weight is probably given to the initial low temperature, since little sweat is produced from an unacclimatized subject until the skin temperature is raised considerably.

Rectal Temperature and Pulse Rate.—Rectal temperature (clinical thermometer inserted for two minutes) and pulse rate (counted for half a minute with the subject in a standing position) were taken initially and immediately after each work period.

Results

Observations During Acclimatization.—In all subjects the usual phenomena associated with acclimatization were observed. As the days passed the sweat rate increased and the final rectal temperature decreased (Fig. 1); moreover, as Table 1 shows, in subjects N and Ba (days 1 to 6) the average skin temperature of the general body surface as well as that within the arm bag fell during acclimatization. These accompaniments of acclimatization are now well established (Newburgh, 1949). Robinson, Turrell, Belding, and Horvath (1943) showed, and we have frequently confirmed in experiments carried out in the climatic chamber in Oxford, that about 80% of the changes in sweating, body temperature, and pulse rate occurred in the first seven days of exposure. It is obvious therefore that the first week or two of daily exposure to heat are the crucial ones for examining sweat for changes brought about by acclimatization. It will be noted (Fig. 2) that during the first week of acclimatization on a high salt diet Ba's weight (as measured in the morning before entering the hot room) increased from 76·4 to 77·5 kg. This may well be due to the rapid increase of blood volume reported by Bazett, Sunderman, Doupe, and Scott (1940) in confirmation of a phenomenon first noted by Barcroft, Meakins, Davies, Scott, and Fetter (1923).

During the week on a low salt diet Ba's weight fell by 3·5 kg. to 74·0 kg., and at the same time his acclimatization appeared to be impeded in so far

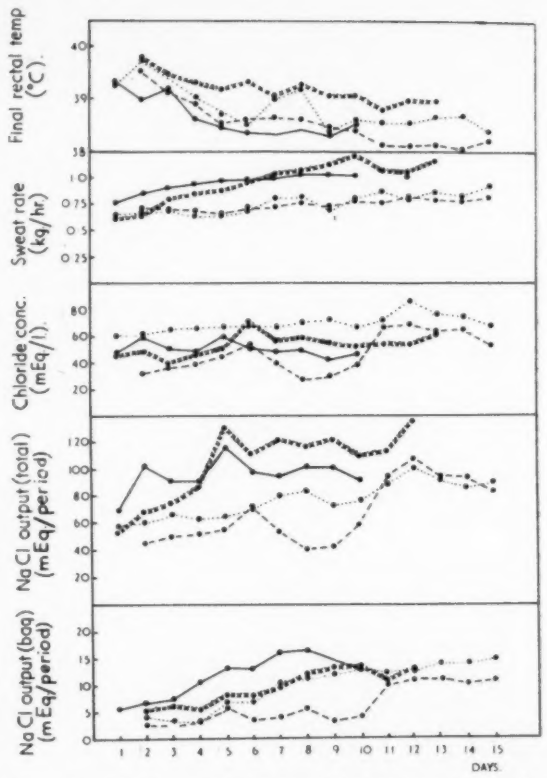


Fig. 1.—(*a*) Final rectal temperature, (*b*) sweat rate, (*c*) chloride concentration of body sweat, (*d*) NaCl output in body sweat, (*e*) NaCl output in arm bag sweat on successive days of acclimatization.
Subject N = xxxxx. Subject Br = ... Subject D = - - - -
Subject C = ————

as the average rectal temperatures, skin temperatures, and pulse rate were higher than in the preceding week (Table 1), and his general condition was poorer. Ordinarily a most energetic person, the subject was now apathetic, complained of fatigue, and, on the last days, of headache during work. The sweat rate nevertheless continued to increase slowly (Table 1 and Fig. 2). When salt was replaced in the diet the rectal temperature fell below the level of the two preceding weeks and the skin temperature also decreased; sweat loss still continued to increase. These findings support those of Adolph (1947) who states that the loss of salt and body fluid interferes with the temperature regulation of men working in the heat, and are confirmed in detail by Robinson and others (1950) who report that " the men's rectal temperature increased during the second and third days on the low salt intake; . . . as the salt deficit was restored, temperature regulation was restored again; . . . their heart rates during work in the heat were raised during the

TABLE I

EFFECT OF ACCLIMATIZATION TO HEAT (D.B. 46·1° C., W.B. 29·4° C.) ON BA AND N*

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Mon.	Tues.	Wed.	Thur.	Fri.	Sat.	Sun.	Mon.	Tues.	Wed.	Thur.	Fri.	Sat.	Sun.	Mon.	Tues.
								Subject Ba								
Average rectal temperature	38·7	38·3	38·3	38·2	38·4	38·2	—	38·6	38·5	38·6	38·2	—	—	—	37·8	38·1
Sweat rate ..	7·8	8·8	9·9	10·4	12·1	12·3	—	13·1	13·4	13·9	13·1	—	—	—	14·1	15·6
Final pulse rate	—	—	136	126	134	138	—	156	156	168	150	—	—	—	130	136
Average body skin temperature	37·3	—	37·0	36·9	36·9	36·1	—	36·5	36·4	36·5	36·9	—	—	—	36·0	36·2
Average arm skin temperature	38·7	—	38·0	38·0	37·9	36·9	—	38·1	37·0	38·2	39·9	—	—	—	37·5	37·9
								Subject N								
Average rectal temperature	38·4	37·9	38·2	38·4	37·9	—	—	38·1	37·9	—	—	—	—	—	—	—
Sweat rate ..	10·2	11·0	12·3	15·0	14·4	—	—	15·9	14·9	—	—	—	—	—	—	—
Final pulse rate	160	152	152	148	152	—	—	140	128	—	—	—	—	—	—	—
Average body skin temperature	36·5	35·9	35·9	36·3	35·9	—	—	36·0	35·7	—	—	—	—	—	—	—

*Temperatures are measured in °C, sweat rates in ml./min., and pulse rate in beats/min. On Days 7–12 Ba was on a low salt diet.

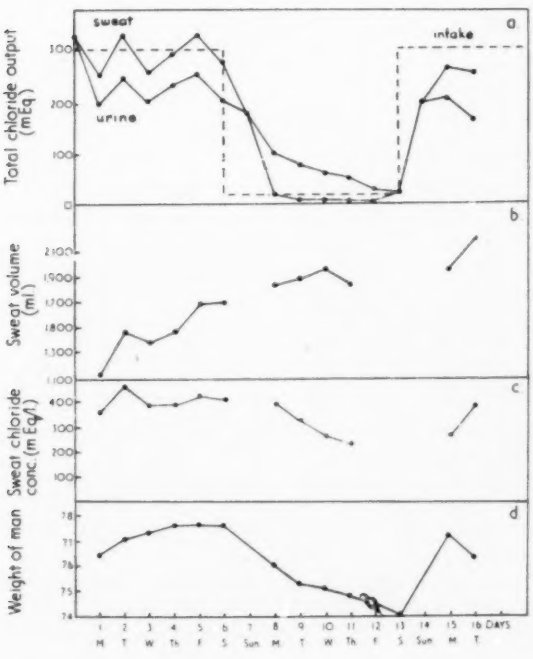


Fig. 2.—In subject Ba, (*a*) total chloride output in urine, and in sweat and urine; (*b*) total volume of body sweat produced in two hours; (*c*) chloride concentration of this sweat; and (*d*) the morning weight of subject daily throughout acclimatization to heat. The intake of chloride in the diet was about 300 mEq. on days 0 to 6 inclusive, and 13 to 16 inclusive; on days 7 to 12 it was 16 mEq.

period of deficit and then lowered again after the salt intake was increased." It seems certain that salt deficit can interfere with the process of acclimatization.

General Body Sweat.—When acclimatization was induced on a high salt diet the chloride concentration showed no sustained change (Fig. 1); the level fluctuated from day to day but there was no suggestion of any decrease in chloride concentration. This is in accordance with the findings of Robinson and others. In view of the progressive increase in sweat loss, the total salt loss in fact increased (Fig. 1), so that on a high salt diet no conservation or restriction of salt by the sweat gland occurs during acclimatization as already pointed out by Black, McCance, and Young (1944).

The results of the experiment on subject Ba are summarized in Fig. 2. During the first week (days 1 to 6) chloride in the sweat remained fairly constant. The total salt output in sweat plus urine also remained fairly constant while the sweat rate increased from day to day. On the first day of exposure in the next week, that is the second day on which the diet was low in chloride, there was no reduction in either concentration or total output of sweat chloride, but the output of chloride in the urine was greatly reduced. On the following three days, however, the chloride level in the sweat fell steadily day by day while the output in the urine became negligible. (On Friday, day 12, the last day on which the low chloride diet was eaten, the subject worked in the hot room at a lower environmental temperature; the chloride concentration of the sweat is omitted as it is not comparable with the rest.)

On the Monday of the third week (day 15), the third day that the supplemented normal diet had been resumed, the sweat chloride was still low, but on the following day it had returned to its former level. The overall output of chloride in sweat plus urine was only a little below the probable level of intake on this day. The findings of Robinson and others are entirely in agreement with these results in showing that a decrease in chloride concentration may be induced late in the acclimatization period, and is not an essential part of it but depends on the level of salt intake.

Arm Bag Sweat.—When the chloride concentration and output are followed during acclimatization in sweat collected from arm bags, two peculiarities are noted, which we attribute to the presence of the bag (van Heyningen, 1951). First, the output of sweat in the arm bag increases as it does in general body sweat, but the increase is relatively far greater. The total sweat rate of all the four subjects on a high salt intake had increased by the tenth day of exposure by increments varying from 21% to 98% while the sweat rate from the arm had increased by increments varying from 235% to 288%. As shown in Fig 3 on four subjects, the ratio of volume of body sweat to volume of arm sweat decreased over the same period from between 30 and 50 to about 15, a value close to that arrived at indirectly from an analysis of the regional distribution of sweating (Weiner, 1945). The fifth subject, Ba, gave a very similar result. Secondly (Fig. 4) the chloride concentration of arm bag sweat, as of the other constituents, lactate and urea, (Weiner and van Heyningen, 1949) falls with acclimatization even on a high salt diet, whereas the general body sweat shows no trend in this respect. Nevertheless the daily output of salt from the arm bag, like that from the general body surface,

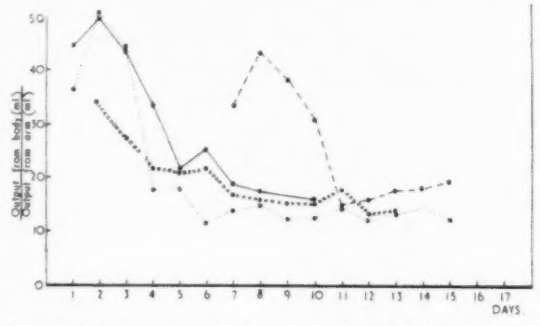


Fig. 3.—The ratio on successive days of acclimatization. Total volume output from body : total volume output from arm. Subject N = xxxxx. Subject Br = ... Subject D = - - - - - Subject C = ————

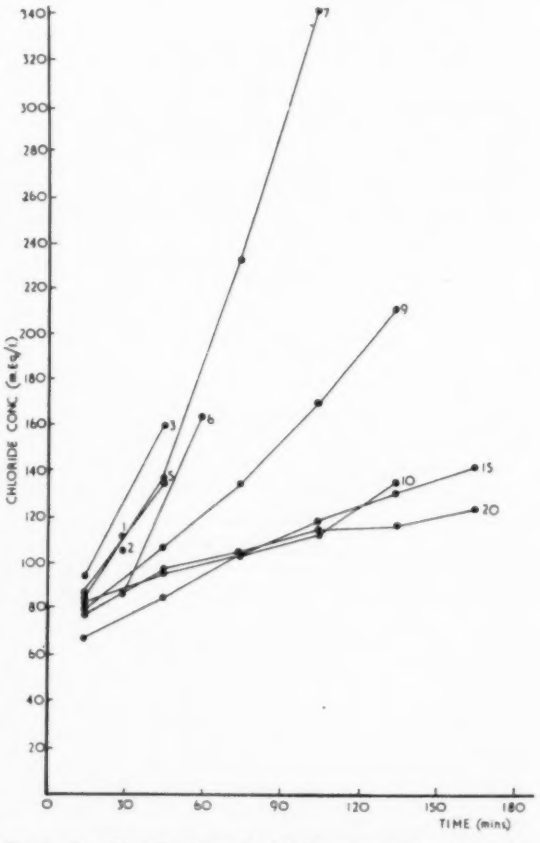


Fig. 4.—In subject Br change in chloride concentration of arm bag sweat during exposure throughout acclimatization. The numbers on the curves are the serial days of exposure. The subject's diet was supplemented with NaCl daily.

does not fall but increases (Fig. 1). The fall in chloride concentration in arm bag sweat is due solely to the very large increase in output of water within the arm bag during the acclimatization period. When the subject goes on to a low chloride intake the concentration of salt in arm bag sweat does, in fact, fall, as Ladell (1945) observed. A fall in concentration of arm bag sweat is therefore found both as a result of acclimatization and of low salt intake. Although the fall in concentration on a high salt intake does not indicate a conservation of salt, it appears to run more or less parallel to the acclimatization process. This is well illustrated by experiments (Table 2) in which a comparison of the composition of sweat, obtained in six different thermal environments before and again after acclimatization, was made on a subject, H. The six initial exposures were made at the rate of only two a week to ensure as far as possible that the subject remained unacclimatized to heat. He was acclimatized by repeated exposure between August 23 and September 10. Table 2 shows, in conformity with the results already described, that the "post-acclimatization" exposures always yielded sweat of a lower chloride content. The overall sweat rate was increased in five cases out of six and the rise in rectal temperature was always decreased.

TABLE 2

COMPARISON OF ARM BAG SWEAT IN SUBJECT H IN VARIOUS ENVIRONMENTS BEFORE AND AFTER ACCLIMATIZATION

Date (1948)	Environments			Sweat Chloride (mEq./l.)	Rectal Temperature (Rise in 2½ hr. °C.)	Overall Sweat Rate (ml./min.)
	D.B. (°C.)	W.B. (°C.)	A.M. (ft./min.)			
July 13	37·5	32·0	75	155	1·4	7·5
Sept. 15	..	..	..	148	0·8	21·3
July 23	51·5	27·5	100	153	1·2	14·9
Oct. 1	..	..	..	119	0·2	15·5
July 27	32·0	32·0	135	111	0·3	7·6
Sept. 27	..	..	..	99	0·2	8·5
July 29	43·5	31·0	20	178	1·6	19·7
Sept. 30	..	..	..	113	0·3	13·3
Aug. 5	35·0	27·0	75	131	0·2	6·8
Sept. 14	..	..	..	92	0·0	7·5
July 15	43·5	31·0	50	163	2·5	11·2
Sept. 24	..	..	..	124	0·3	15·7

Salt Loss of Unacclimatized Subjects.—Table 3 gives the results for two subjects. The total chloride loss in the sweat increased as the conditions became more severe. In spite of the loss of chloride in the sweat, the two and a half hour loss of chloride (sweat plus urine) was on an average much lower than that on the control days when there was no exposure to heat. In Mol, one of the subjects, the average chloride output in the urine on the eight control days was 224·4 mEq.; on the 10 days on which he was in the hot room the average output was 124·7 mEq. in sweat and urine. In Mac, the second subject, the average chloride output on the eight control days was 244·4 mEq. and on the eight days on which he went in the hot room it was 174·2 mEq.

A t test indicates that in subject Mol the difference between the means of the two series is highly significant, $P = 0{\cdot}001$ (difference between means = 99·7, degrees of freedom = 16, $t = 5{\cdot}25$). For subject Mac, P is just below the 5% level of significance (difference between means = 70·2, degrees of freedom = 14, $t = 2{\cdot}05$). These results show that the total loss of chloride on days on which sweating occurs did not exceed the loss on days when no heat exposure took place, and in the case of subject Mol it was decidedly less. In subject Mac, although a reduction is also present, it is statistically barely significant. In both subjects it is clear that the kidney restriction has been sufficient to compensate for the sweat salt loss.

Discussion

The foregoing experiments are in agreement with those of Black and others (1944), Conn and others (1946), and Robinson and others (1950) in affirming that a reduction in the chloride concentration (and

output) of body sweat occurs only when the intake of dietary salt is insufficient to prevent the occurrence of a negative salt balance induced by sweating. It is very likely that this process of adjustment underlay the original observations of the phenomenon by Dill, Jones, Edwards, and Oberg (1933). The " salt conservation " response is not a necessary part of the acclimatization process ; it may be induced after the individual has been in the heat for shorter or longer periods, as in our experiments, and in those of Robinson and others or, as has been shown, it may be entirely absent in the acclimatization period if the salt intake is maintained at a high level. The fact that on a high salt diet the sweat chloride concentration in arm bag sweat (unlike general body sweat) falls, is not an indication of salt conservation. As we have shown, the salt loss does not decrease. The fall in arm bag sweat concentration is bound up with the acclimatization process itself since it is attributable to the very large increase in sweat loss within the arm bag.

The reason for the relatively greater increase in output of sweat within the arm bag during acclimatization is not known, but must, in some way, be due to the higher temperature and humidity therein.

The response to a salt deficit by the sweating man leading to the re-establishment of salt balance has been analysed in some detail by Conn (1949a). When his subjects, who were on a constant diet containing 14·5 g. NaCl (248 mEq.) a day, were first introduced into the hot room, there was a sharp fall in the urinary loss of chloride. This was followed on the next day by a sharp fall in the chloride concentration of sweat, the total loss of salt by this route being greatly reduced. The urinary excretion then gradually rose until an equilibrium between intake and losses in sweat and urine was established after about five days. On a daily intake as low as 52 mEq. Robinson's subject was near to establishing an equilibrium on the fourth day. Whether our subject Ba (Fig. 2) on a still lower intake (16 mEq.) could have done likewise is not certain ; it would have required a negligible output of chloride in the urine and a sweat chloride concentration of about 7 mEq./l. Sweat of nearly this dilution has been reported by both Conn and Robinson. By the fourth day the chloride concentration had not in our subject fallen below 20 mEq./l., though the daily deficit was progressively lessening (Fig. 2). The total drain of salt from the body over these four days amounted to about 300 mEq. of NaCl. As McCance (1936) showed, salt deficiency is accompanied in its first stages by a corresponding water loss, the effect of which is to preserve for the time being the normal osmotic pressure.

In combating a threatened salt deficiency the response of the kidney is extremely prompt and precedes that of the sweat gland, as shown by Conn (1949a). The prompt response of the kidney in restricting salt loss seems to us, on the basis of the results in our section on the partition of chloride between sweat and urine in unacclimatized subjects, to be a reaction of exposure to heat *per se*. These experiments show that the occasional exposure to heat of unacclimatized subjects, with its consequent loss of chloride in the sweat, brings about a compensatory reduction of urinary chloride so great that the total loss of chloride may be actually less on these days than on the days when the subject was not exposed to heat (Table 3). Furthermore, this compensatory response demonstrates that when subjects were acclimatized to heat on a high salt diet there was no possibility of a negative balance occurring to stimulate the reduction of sweat chloride concentration. The operation of such a " chloride saving mechanism " was postulated by Lee and Mulder (1935) but further experiments seemed to Lee, Murray, Simmonds, and Atherton (1941) to throw some doubt on its existence. Their subjects spent six to seven hours daily in the hot room, but the chloride excretion during the remainder of the 24 hours, when the subjects were not in the hot room, was not measured ; it is during this time that the sparing mechanism operated in the present experiments. As in Lee's experiments, the volumes of urine excreted in the hot room were too low to determine at what stage the sparing mechanism began to operate. It was during the remainder of the 24 hours after the subject had left the hot room that the reduction in urinary chloride output was manifested.

The regulatory processes underlying these kidney and sweat gland responses are not yet clearly established. Current hypothesis favours the involvement of the adrenal cortex, and this has received support from experiments by Conn and others (1946) and Robinson (1949) who have shown that desoxycorticosterone acetate reduces the chloride of general body sweat, as suggested earlier by Laddell (1945) and Moreira, Johnson, Forbes, and Consolazio (1945) using arm bag samples. Conn (1949 a and b) believes that the adrenal cortex activity is mediated through the adreno-corticotrophic hormone of the pituitary.

During a period of salt deficit in the heat the subject experiences not only an interference with heat regulation, as intimated above, but also subjective distress, despite preceding acclimatization. These reactions were noticeable in our study and

TABLE 3

SALT LOSS OF TWO UNACCLIMATIZED SUBJECTS

Environment			Chloride (mEq.) Loss During and After Hot Room				Chloride Loss (mEq.)
D.B. (°C.)	W.B. (°C.)	R.H. (%)	Sweat	Urine Passed in Hot Room	24-Hour Loss in Urine	24-Hour Loss in Sweat and Urine	24-Hour Loss in Urine on Control Days
				Subject Mol			*Mol*
23·8	23·8	100	1·9	9·6	107·2	109·1	183
30·5	21·1	40	6·8	24·3	97·0	103·8	185
34·4	23·8	40	9·4	25·5	67·9	77·3	195
27·7	27·7	100	9·6	2·6	133·9	143·5	195
30·5	30·5	100	16·8	25·0	97·7	114·5	229
37·2	26·1	40	22·1	5·1	83·5	105·6	239
38·8	27·7	40	32·0	32·2	165·7	197·7	272
38·8	27·7	40	34·7	14·2	75·5	110·2	297
33·0	33·0	100	46·0	17·8	135·0	181·0	..
37·8	34·5	80	47·9	28·7	57·5	105·4	..
				Subject Mac			*Mac*
24·4	15·5	40	2·2	48·7	204·7	206·9	119
26·1	26·1	100	2·9	33·8	172·6	175·5	195
27·7	27·7	100	5·3	117·4	192·5	197·8	218
30·5	30·5	100	14·9	29·6	137·7	152·6	226
38·8	27·7	40	34·9	19·6	132·2	167·1	227
43·3	30·5	40	62·3	7·8	63·6	125·9	244
33·0	33·0	100	77·6	10·8	77·0	154·6	287
43·3	30·5	40	81·9	34·7	131·0	212·9	439

Sweat and urine were collected over two hours in the hot room. Urine was collected over the following 22 hours.

in that by Robinson ; the latter found that a return to salt improves the individual's condition noticeably. There is a strong presumption from McCance's studies (McCance, 1936 ; Black, McCance, and Young, 1944) that the distress and inefficiency are closely bound up with both osmotic and circulatory disturbances. During the period of " negative " salt balance the conditions of osmotic imbalance favouring heat cramps must exist. If the salt deficit is not corrected either by physiological adjustment or by dietary intake, there ensues a strong liability to the syndrome described by McCance (1936) as well as to heat cramps when working in the heat.

On the basis of present knowledge it seems desirable to continue the generally accepted policy of salt supplementation for men exposed to heat. For it cannot be assumed from the available data that the general condition on a low salt diet improves when salt balance is eventually re-established. Taylor and others (1943) have found a marked deterioration both in working ability and in postural adjustment on a salt intake of 6 g. a day compared with 15 g. when subjects were tested in the hot room daily over periods of two or three days. Another consideration in favour of a relatively high salt intake is the likelihood that large individual differences exist in the ability of the sweat gland and the kidney to restrict salt losses. Adolph (1947) has drawn attention to the strikingly greater sweat salt output of some men in desert climates. Ladell and others (1944) make the suggestion that cases of salt deficiency with dehydration (with vomiting and cramps) are found in individuals who habitually excrete sweat of too high salt concentration.

In conditions where men sweat fairly profusely, say at a water output of 5 l. a day and over, it would be reasonable to estimate a loss of 3 g. of salt per working hour and about 0·3 to 0·5 g. per hour during recovery and at rest. Near the upper limit of tolerance, i.e., four hours' activity in the heat producing 4·5 litres of sweat, the daily requirement would then be about 20 to 24 g. of salt. This figure is close to the average intake, as actually measured, of men working in tropical climates (Molnar, Towbin, Gosselin, Brown, and Adolph, 1946). It would necessitate in most cases a supplement of about 10 g. to the salt in the usual diet. Methods of administration of salt in industry have been dealt with by Stewart (1945).

Summary

The sweat and urinary loss of chloride have been studied in individuals working in hot conditions for short periods.

Acclimatization to heat is only accompanied by a decrease in the chloride concentration of general body sweat if a negative chloride balance is induced by restriction of the chloride intake.

Sweating for short periods (two hours) in unacclimatized subjects brings about a compensatory reduction of urinary chloride manifested after the subject leaves the hot room. This reduction is so great that the total loss of chloride may be less on days on which sweating occurs than on the control days.

Attention is drawn to the limitations to the use of sweat collected in arm bags as a method of assessing the bodily salt balance.

The bearing of these findings on the desirability of supplementing the salt intake in the diet is discussed.

Our best thanks are due to the subjects, and in particular to Mr. R. Baldock for cooperation in these investigations.

References

Adolph, E. F., ed. (1947). "Physiology of Man in the Desert." New York.

Barcroft, J., Meakins, J. C., Davies, H. W., Scott, J. M. Duncan, and Fetter, W. J. (1923). *Phil. Trans. Roy. Soc.* B **211**, 455.

Bazett, H. C., Sunderman, F. W., Doupe, J., and Scott, J. C. (1940). *Amer. J. Physiol.*, **129**, 69.

Belding, H. S., Darling, R. C., Griffin, D. R., Robinson, S., and Turrell, E. S. (1945). In "Clothing Test Methods", edited by L. H. Newburgh and Milton Harris. Michigan.

Black, D. A. K., McCance, R. A., and Young, W. F. (1944). *J. Physiol., Lond.*, **102**, 406.

Conn, J. W. (1949a). *Advanc. intern. Med.*, **3**, 373.

——, (1949b). *Arch. intern. Med.*, **83**, 416.

——, and Johnston, M. W. (1944). *J. clin. Invest.*, **23**, 933.

——, ——, Louis, L. H. (1946). *Ibid.*, **25**, 912.

Dill, D. B., Jones, B. F., Edwards, H. T., and Oberg, S. A. (1933). *J. biol. Chem.* **100**, 755.

Ladell, W. S. S. (1945). *Brit. med. Bull.*, **3**, 175.

——(1949). *Lancet*, **2**, 836.

——, Waterlow, J. C., and Hudson, M. F. (1944). *Ibid*, **2**, 491, 527.

Lee, D. H. K., and Mulder, A. G. (1935). *J. Physiol., Lond.*, **84**, 410.

——, Murray, R. E., Simmonds, W. J., and Atherton, R. G. (1941). *Med. J. Aust.*, **2**, 249.

McCance, R. A. (1936). *Lancet*, **1**, 643, 704, 765, 823.

Molnar, G. W., Towbin, E. J., Gosselin, R. E., Brown, A. H., and Adolph, E. F. (1946). *Amer. J. Hyg.*, **44**, 411.

Moreira, M., Johnson, R. E., Forbes, A. P., and Consolazio, F. C. (1945). *Amer. J. Physiol.*, **143**, 169.

Moss, K. N. (1923). *Proc. roy. Soc.* B, **95**, 181.

Newburgh, L. H. (1949). Editor, "*Physiology of Heat Regulation and the Science of Clothing*." Philadephia and London: W. B. Saunders Co.

Robinson, S. (1949). In "*Physiology of Heat Regulation and the Science of Clothing*", edited by L. H. Newburgh. Philadelphia.

——, Kincaid, R. K., and Rhamy, R. K. (1950). *J. appl. Physiol.*, **2**, 399.

——, ——, ——(1950). *Ibid.*, **3**, 55.

——, Turrell, E. S., Belding, H. S., and Horvath, S. M. (1943). *Amer. J. Physiol.*, **140**, 168.

Stewart, D. (1945). *British Journal of Industrial Medicine*, **2**, 102.

Talbott, J. H. (1935). *Medicine, Baltimore*, **14**, 323.

Taylor, H. L., Henschel, A. F., Mickelsen, O., and Keys, A. (1943). *Amer. J. Physiol.*, **140**, 439.

Van Heyningen, R. E. (1951). "Adaptation of Men to Hot Climates with Reference to Sweat Gland Activity and Sweat Composition". D.Phil. Thesis, Oxford.

Weiner, J. S. (1945). *J. Physiol., Lond.*, **104**, 32.

——, and Van Heyningen, R. (1949). *Nature, Lond.*, **164**, 351.

Brit. J. industr. Med., 1952, **9**, 65.

PENETRATION OF DUST PARTICLES AND SITES OF DUST STORES IN PNEUMOCONIOSIS

BY

GIACOMO MOTTURA

From the Institute of Pathological Anatomy and Histology of the University of Pisa

The statements of many authors on the problem of the penetration of dust particles into the connective tissue of the lung appear to contradict the results obtained from morphological and experimental observations.

Many writers, noting the frequent appearance of dust cells in the lumen of the alveoli and their apparent resemblance to dust-laden cells in the interstitial deposits in pneumoconiosis, accept the view that the endoalveolar phagocytes loaded with inhaled dust actively penetrate the alveolar walls by amoeboid movement, and hence work their way into the connective tissue and into the lymph channels, as far as the storage sites.

The study of the alveolar dust cells has been too closely bound up with histological questions about alveolar lining and with its embryological derivation. It seems unnecessary to decide whether or not a phagocyte is endodermal in origin before admitting that the phagocyte itself acts as an epithelial cell. I think I can leave out this aspect of the discussion, making a distinction between the problem of the origin and the nature of the alveolar phagocytes, and the participation of these cells in the absorption of dust in the connective tissue spaces of the lung.

Many experimental and morphological studies demonstrate that the activity of the dust cells is mainly evident on the surface of the bronchiolo-alveolar spaces.

Several facts must be borne in mind. The phagocytosis of substances, inhaled or inoculated into the trachea, takes place with a rapidity (about 10 minutes) that demonstrates the superficial position of the phagocytes. This proves that they are not of migratory origin from the connective tissue spaces or from the blood (Arnold, 1880; Seemann, 1931; Westhues and Westhues, 1925; Huguenin and Delarue, 1929; Businco and Giunti, 1930). Even the granulocytes which are especially adapted to migration, take more time to migrate (Huguenin and Delarue, 1929; Aschoff, 1936) when an exudative lesion occurs.

The intracellular deposition of particles on the alveolar walls is of a temporary character. The cells engaged in phagocytosis rapidly become swollen and detached, and are carried away by the mucous flow, both secretory and expulsive, originating from the bronchioles. This process of detachment is partly related to the rate of the intracellular storage of particles, but is favoured by possible inflammatory exudative complications (Huguenin and Delarue, 1929), by alveolar collapse and by the presence of free fluid in it (Westhues and Westhues, 1925). In fact, fixation of the lung extracted from the thorax by intratracheal injection artificially increases the phenomenon of detached dust cells (Macklin, 1950 and 1951).

This process leads chiefly to expulsion via the bronchi. Some of the inhaled particles, however, reach the pulmonary lymph flow. This occurs almost instantaneously. Blood aspiration in the lungs experimentally observed in animals (Nothnagel, 1877) or accidentally in man through rupture of an aortic aneurysm into the trachea (personal observation) is accompanied by the presence of red cells in the pulmonary lymph channels. The time in which this process takes place, measured also with special experiments of intratracheal inoculation, is sometimes less than 10 minutes. This time is too short for it to have occurred through a phagocytosis on the alveolar surfaces (Gillilan and Conklin, 1938).

Later, but not before two or three hours after the inhalation or inoculation into the trachea of particulate matter, particles are seen inside the cells in the peribronchiolar or periarterial connective tissue (Huguenin and Delarue, 1929). Some writers believe that these cells have migrated from the alveoli by their own movement or through passive transport in the lymph, although it is difficult to imagine that cells in an epithelial position,

or free in the alveolar lumen, could penetrate actively into the interstitium.

The phagocytic content gives rise to a change in the shape of the cytoplasm which becomes globular. Although, as far as I am aware, precise studies are lacking on the subject, this change corresponds with a diminution of those qualities of the surface which go to determine the character of amoeboid activity. I agree with Macklin (1950) that the dust cells quickly become spent phagocytes which are incapable of movement and destined to a passive external elimination. It is admissible that some phagocytes from the alveolar lumen may enter the connective tissue. The process may, however, be similar to that observed in the case of some other substances, such as dust particles or red cells, which can definitely be absorbed without migratory phenomena. I have, in exceptional cases, found in the regional lymph nodes of workers who have died from pulmonary asbestosis, some asbestos needles, about the length of 20 cells ; in such cases a passive transport by the lymphatic flow is the only admissible form of transport.

Other writers, while recognizing the impossibility of endocellular transport from the alveolar lumen to the connective tissue, believe that the migration of the phagocytes occurs within the limits of the pulmonary connective tissue spaces, as far as the permanent storage depots. This view corresponds with a current opinion, although positive evidence is entirely lacking. The fact that in the permanent interstitial deposits the dust is incorporated in cells, does not demonstrate that transport has occurred by means of those cells.

However, several observations are in favour of the metastasis of naked particles by means of the lymphatic flow. Akazaki's (1936) experimental findings with the inhalation of soot and powdered quartz should be particularly borne in mind. I, too, have noted in research on human pneumoconiosis that phagocytes in migratory posture or with strangled cytoplasm are never seen in the connective tissues, and that only plump phagocytes are present. I have also noted that, whereas phagocytes are usually not seen on the interalveolar walls, they are present in the permanent interstitial deposit. However, isolated anthracotic particles or naked quartz crystals (recognizable by their double refraction) are often found on the interalveolar walls in patients with silicosis.

Thus there is considerable evidence, although partly negative and indirect, against the hypothesis of endocellular migratory transport of dust. This leads to the admission that transport in the form of naked particles prevails. However, even this concept has not been completely worked out as yet.

A particle of dust, having once reached a lymph channel, may be transported by the lymph flow as far as a lymph node or even into the blood. At lymph node level, it may easily be arrested and hence enter the lymphoreticular tissue of the lymph node itself. At first, it is included in a reticulum cell of the lymph sinus, then this cell sinks into the underlying lymphoreticular tissue, probably not as a result of active migration, but because the other cells on the walls of the sinus (reticulum cells and lymphocytes) grow through an ordinary reactive hyperplastic process. In fact, the lymph node in the course of its life usually grows at the periphery, particularly in the vicinity of the peripheral sinuses, whereas it becomes atrophic centrally and at the hilum. The phagocytes of the sinus, when loaded with particles, take little or no part in the growth, and remain fixed to the old stroma which gradually becomes sclerotic and withdraws, while the active hyperplastic parts advance towards the periphery. Therefore the anthracotic lesion is concentrated far from the sinuses. Analogous phenomena occur in silicosis in the lymph nodes, although disturbed by sclero-hyaline changes (Mottura, 1936, 1938).

A process of this kind seems to occur only in the lymph nodes or in granulation tissue, and is probably impossible on the surface of the pulmonary alveoli, where primary penetration of dust into the interstices occurs without hyperplastia.

The pulmonary alveolus is covered by a superficial fluid veil which, at any rate where the wall is practically free of cells, must be physically continuous with the interstitial fluid. The foreign bodies which escape from the phagocytic barrier remain incorporated in this film, as in a foam bubble, and are possibly carried into the interstitial flow.

Further, it is well known that the lymph channels of the lung originate not in the interalveolar walls, but in the adventitial connective tissue of the bronchioles and the terminal branches of the arterioles (Miller, 1947 ; Luna, 1937 ; Ottaviani, 1938). On the other hand, it is universally admitted that the entry of the particles occurs at the alveolar surface. Thus an interstitial space exists, and extends from this surface as far as the origin of the lymph channels. Here lymph exists in the form of interstitial fluid, not canalized but rather retained according to McMaster and Parsons' (1939) idea of connective tissues in general. Here, as in other connective tissues, it must be admitted that fibrous structures, microscopically visible, such as reticular fibres (Volterra, 1927 ; McMaster and Parsons, 1939), or even fibrous ultramicroscopic multimolecular structures (Frey-Wyssling, 1948), guide the interstitial fluids. Free fluid reaches the surface only

as oedema or canalized lymph. The particles necessarily follow this flow before being admitted into the lymph channels. This is the most difficult point to understand, but an explanation in these terms does not seem impossible, whereas the postulate of an active migratory cellular mechanism does not make it clearer.

All connective tissue, faced with foreign matter, such as dusts inoculated by tattooing, red cells, etc., shows an increase in lymphatic drainage, so that, under many conditions, the origin of the lymph channels must be considered as functionally open to the entry of even very bulky impurities. The pulmonary connective tissue, in comparison with that of other organs, is much more easily invaded by external substances, e.g. in the common condition pneumoconiosis caused by soot or quartz.

Phagocytosis in the connective tissue of the lung usually occurs when the particle has already passed the interval corresponding with the interalveolar walls. In experimental pneumoconiosis in animals and in man, all investigators note that the interalveolar walls are almost always free of phagocytes. Thus, it may be affirmed that the incorporation of dust particles in the interstitial cells occurs as a temporary stage or as a permanent deposit in sites different from the interalveolar walls, where entry from outside occurs.

In early experiments on anthracosis from soot (Ruppert, 1878 ; von Ins, 1878) it was noted that the dust-laden cells were found with some regularity where the pulmonary connective tissue was thickest, and especially around the large blood channels. It was thought that this corresponded with particular regions of the lymph apparatus. This hypothesis was forgotten until it reappeared in the works of Gardner, 1933, and of Simson and Strachan, 1931.

Simson and Strachan (1931) made a plastic reconstruction by means of serial sections of pulmonary tissue from a case of status lymphaticus. They found that peripheral accumulations of lymphocytes were situated mainly in three areas : in the connective tissue between the bronchioles and the adjacent branches of the pulmonary artery ; at the junction of the small veins of the primary and secondary lobules with the large branches of the pulmonary vein ; and along the course of the pulmonary artery and in the connective tissue below the pleura. They thought that in pneumoconiosis these areas were collection sites for the phagocytes migrated from the lymph channels. However, no confirmation of this hypothesis was obtained.

Later, Simson (1935) reconstructed two pieces of lung containing silicotic nodules. He pointed out the relation between the nodule and the branching respiratory bronchioles. (Furthermore, in the photographs of the models, arterial branches can be seen in the centre of the nodules.) He did not find any branches of the pulmonary veins related to the nodules. The writer abstained from precise references to lymph tissue, and declared that he found great difficulty in identifying this amongst the gross changes due to silicotic sclerosis.

I took up the problem, in collaboration with Dulbecco, by means of reconstruction models of serial sections of non-sclerotic pneumoconiosis, for example, anthracosis and simple siderosis, and of nodular silicosis in early stages, in various cases and with varying magnifications (Mottura and Dulbecco, 1946 and 1947 ; Mottura, 1951).

In anthracosis and siderosis, we found intracellular deposits selectively situated in the adventitial connective tissue of the distal branches of the pulmonary artery and of the corresponding respiratory bronchioles of all sizes. That is to say, these deposits are contained in strands of axial connective tissue of the secondary and primary lobules, while the alveolar connective tissue and, for the most part, the interlobular connective tissue, remain undamaged.

In nodular silicosis of iron moulders the intracellular dust deposits were found not only in the same axial positions in the lobules, but also around the lobules. In silicosis, as is well known, a greater development of the connective tissue occurs in relation to the deposits. The changes, which make the picture difficult to interpret, are derived from this and from the increased emphysema which occurs besides the sclerotic centres (perisclerotic emphysema, Mottura, 1941). Axial sclerosis, particularly in periarterial and peribronchial areas, appears in the form of strands swollen into nodules due to focal hyaline transformation. The silicotic nodules preferentially tend to be situated at the beginning of these axial sclerotic strands, that is, at the junction of the relatively undamaged interalveolar connective tissue with the periarterial and peribronchiolar connective tissue, where, ascending the bronchiol-alveolar tree, the dust deposits begin to appear (Fig. 1).

Interlobular sclerosis, that is sclerosis peripheral to the lobule, appears as extensive and thick sheets of dense connective tissue, which include the vein branches. It is known that these, in fact, usually run between the lobules (Miller, 1947). The larger sclerotic sheets (between the secondary lobules) give off branches which may take the form of cusps, ascend along the vein branches between the primary lobules, and can be followed in serial sections until they join up with the axial sclerosis. These branches accompany the small venous channels, described by Miller (1947), originating

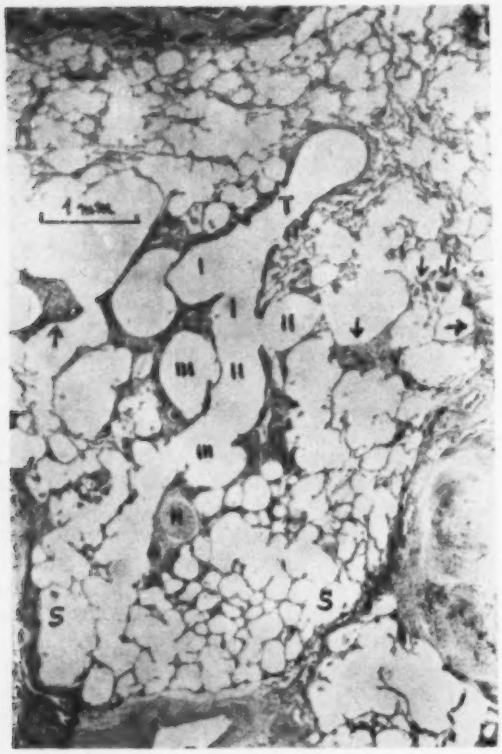


FIG. 1.—Section of a secondary lobule from a silicotic lung (simple nodular silicosis in a moulder).

T = terminal bronchiole.
I, II, III = respiratory (alveolar) bronchioles of first, second, and third order. (They correspond to the axial sclerosis in the lobule.)
N = silicotic nodule at the end of the bronchiolar tree.
S = interlobular sclerotic septa (peripheral laminar sclerosis in the lobule).
The arrows show sclerotic perivenous strands, which join radially the interlobular sclerosis with the axial one.

from the lobular axis and extend to its periphery, and perhaps correspond with the anastomotic arterio-venous branches which run radially within the lobules. In these sites of laminar interlobular sclerosis, the hyaline changes are mostly diffuse and not nodular, although true nodules are observed, particularly at the apex of the branches directed radially towards the axis of the lobule. Therefore, I distinguish two fundamental topographical components of silicotic sclerosis : axial sclerosis of the secondary and primary lobules, in the form of strands and nodules (periarterial and peribronchiolar) ; and interlobular sclerotic sheets between the secondary lobules (perivenous), with radial projections between the primary lobules which may join the interlobular sclerosis with the axial sclerosis. Interlobular sclerotic sheets are mainly developed near the pleura. It is clear that all these lesions follow the course of the lymph channels, the latter running chiefly in the adventitia of the axial (arteries) and peripheral (veins) blood vessels of the lobules.

Wulff (1934) had already pointed out in his observations on silicotic lung sections that the interlobular septa suffer severe fibrous changes and may branch out towards the centre of the lobule. This writer interprets silicosis as an obliterating lymphangitis. He affirms that the drainage of the dust occurs at first along the easiest path of the lymph channels following the roots of the pulmonary vein, therefore the silicotic changes would develop in the first instance and most intensely at the periphery of the lobule, and only afterwards, when the peripheral pathways are blocked, would they advance towards the centre of the lobule.

Contrasting with this interpretation is the fact that in pneumoconiosis caused by inert dusts we found the deposits almost exclusively along the axial lymph channels, which would thus appear to be selectively damaged. Also in early silicosis we found great development of axial sclerosis. Therefore it would appear that the interlobular sclerosis is secondary to the blocking of the principal axial drainage channels, and is due to dissemination of dust along the collateral peripheral pathways. The next question is, Do the pneumoconiotic deposits correspond to certain determined tracts of the pulmonary parenchyma ?

The elective areas of inert dust deposits and silicotic nodules correspond, broadly speaking, to regions where, in certain rodents and occasionally also in man, lymphoid accumulations are found. This correspondence has been noticed by various writers who think that the dust deposits occur in preconstituted lymphoid stations. Nevertheless, in the great majority of human cases, it would be necessary to consider them not so much as lymphoid stations already existent, but rather as hystiocytic hyperplastic foci in predetermined sites. It is important to understand the limits of this predetermination and also their exact relationship with the lymph channels in general.

Clumps of hyperplastic histiocytes are not found in the lymph channels in pneumoconiosis but in the connective tissue in immediate relationship to them, and more precisely in the connective tissue near their beginning. In connective tissue interstices in general, invasion by foreign bodies may be resolved by simple lymphatic drainage. Only particularly irritating or excessively abundant or stagnating substances provoke cellular reactions, including phagocytosis, which expresses the insufficiency of lymphatic drainage, and takes place before the origin of the lymph channels. I think it probable that every accumulation of dust-laden phagocytes is an expression of the impossibility

or inadequacy of a prompt drainage of interstitial accumulations. For this reason pneumoconiosis should not at first be considered as a disease of the lymph channels, but as a disease of the interstitial roots of the lymph channels. Naturally diseases of the lymph apparatus, such as involvement at lymph node level, may afterwards aggravate the situation in the peripheral tissues. Therefore, when we note the electivity of the deposits in the peripheral bronchiolo-arterial field in relation to the origin of the principal lymph channels, we may postulate that this is due to the effect of a concentration of particulate substances, which are difficult to drain, rather than a special predisposition or liability to phagocytic activation in the connective tissue in this field.

When, in the phagocytic accumulation, the dust provokes particular progressive changes, such as hyperplasia of cells and fibrils and hyalinosis, then further hindering factors intervene. Thus the dissemination of the same process along collateral pathways, which run within the interlobular septa, is provoked. The development of this process in silicosis causes the silicotic nodules. In the granulomatous and massive forms, the addition of an early diffuse hyperplasia complicates the process and less characteristic topography results.

The silicotic nodule acquires its specific properties chiefly because of its situation, which usually corresponds to a certain distal tract of the arteriolar and broncho-alveolar branches. This is probably not due to a strict specific property of the tissue, but to an accidental though frequent concurrence of circumstances, which determine the stagnation of interstitial lymph flows at a level where convergence and concentration occur.

References

Akazaki, K. (1936). *Beitr. path. Anat.*, **97**, 439.
Arnold, J. (1880). *Virch. Arch. path. Anat.*, **80** 315.
Aschoff, L. (1936). *Verhandl. deutsch. Gesell. inn. Med.*, **48**, 100.
Businco, A., and Giunti, G. (1930). *Haematologica*, **11**, 499.
Frey-Wyssling, A. (1948). "Submicroscopic morphology of protoplasm and its derivatives," New York-Amsterdam. Trans. by J. J. Hermans and M. Hollander.
Gardner, L. U. (1933). *J. Amer. med. Ass.*, **101**, 594 ; (1937), *J. ind. Hyg. a. Toxicol.*, **19**, 111.
Gillilan, L. A., and Conklin, R. E. (1938). *Amer. J. Physiol.*, **123**, 598.
Ins, A. von, (1878). *Virch. Arch. path. Anat.*, **73**, 151.
Huguenin, R., and Delarue, J. (1929). *Ann. Anat. path.*, **6**, 1181.
Luna, E. (1937). *Riv. Patol. sperim.*, **8**, 70.
Macklin, C. C. (1950). *Proc. Inst. Med. Chicago*, **18**, 78 ; (1951), *Lancet*, **260**, 432.
McMaster, P. D., and Parsons, R. J. (1939). *J. exper. Med.*, **69**, 247, 265.
Miller, W. S. (1947). "The Lung," 2nd ed., Springfield.
Mottura, G. (1936). *Arch. it. Anat. e Istol. patol.*, **7**, 449 ; (1938). *Giorn. R. Accad. Med. di Torino*, **101**, 315 ; (1941). *Assist. soc.*, **15**, n.4 ; (1951). *Med. d. lavoro*, **42**, 81.
Mottura, G., and Dulbecco, R. (1946). *Rass. Med. industr.*, **15**, 82 ; (1947). *Bull. d'histol. appl.*, **24**, 11.
Nothnagel, H. (1877). *Virch. Arch. path. Anat.*, **71**, 414.
Ottaviani, G. (1938). *Morph. Jb.*, **82**, 453.
Ruppert, H. (1878). *Virch. Arch. path. Anat.*, **72**, 14.
Seemann, G. (1931). "Histobiologie der Lungenalveole." Jena.
Simson, F. W. (1935). *J. Path. a. Bacteriol.*, **40**, 37.
Simson F. W., and Strachan, A. S. (1931). *Public. South Afr. Inst. Med. Res.*, No. XXVI 2, 6, vol. 4, p. 231.
Volterra, M. (1927). *Sperimentale*, **81**, 319.
Westhues, H., and M. (1925). *Beitr. path. Anat.*, **74**, 432.
Wulff, H. B. (1934). *Acta path. microb. Scand.*, **11**, 389.

Brit. J. industr. Med., 1952, **9**, 70.

THE EXPERIMENTAL PRODUCTION OF RADIOGRAPHIC SHADOWS BY THE INHALATION OF INDUSTRIAL DUSTS

PART II: ZIRCON ($ZrSiO_4$)

BY

H. E. HARDING and T. A. LLOYD DAVIES

From the Department of Pathology, Sheffield University, and the Industrial Health Unit, Boots Pure Drug Co., Ltd., Nottingham

(RECEIVED FOR PUBLICATION FEBRUARY 2, 1951)

A preliminary report on the toxicology of zircon (Harding, 1948) gave some details of the properties and uses of this substance and suggested that it was extremely inert within the animal body. At the time of the publication of this preliminary report an experiment was almost completed during which rats were exposed to a fairly high concentration (7–25,000 particles per cc. of air) of zircon dust in a chamber. The period of exposure lasted just over three months, and the animals were killed at intervals up to six months thereafter. To our surprise we were unable to find any zircon in the lungs of these animals either by radiography or microscopically. Since it seemed possible that there had been an error which we were unable to identify, we repeated the experiment on two further occasions. Again no zircon, or only very small amounts, could be found in the lungs. The animals were exposed in a chamber with a dust feed of the type described by Lloyd Davies (1946): working with identical techniques before, between, and after these experiments we found no difficulty in demonstrating dust in the lungs of rats exposed to other dusts (e.g., iron oxide, manganese dioxide, beryllium oxide, silica, graphite, talc, cobalt metal) of similar particle size and in similar concentrations.

Because of the difficulty we had experienced in demonstrating appreciable quantities of zircon in these animals, we set up a fourth experiment in which the concentration of dust in the chamber was increased considerably and the period of exposure was also lengthened. It is this fourth experiment that forms the basis of this paper.

Experimental

Twelve rats, aged about 3 months, weighing 109–135 g. each, were exposed to a very high concentration of zircon dust for six hours daily, five days a week for 144 days, and then for eight and a half hours daily, five days a week for 20 days. Atmospheric dust counts with a thermal precipitator were frequently too high to be counted, but when they could be determined they varied between 37,000 and 130,000 particles per cc. of air, usually near the higher figure; 80% of the particles were below 1 μ, and 30% below 0·2 μ: only rare particles over 5 μ were encountered in the counts. One rat died during the experiment and the others were sacrificed at intervals up to seven months after exposure to the dust. The animals were killed and their lungs preserved in an inflated state according to the technique previously described (Lloyd Davies and Harding, 1949). The lungs were later radiographed and sections made from them for microscopic examination. Sections were stained by haematoxylin and eosin, iron haematoxylin and van Gieson, and by Wilder's modification of Foot's reticulin stain.

Results

The radiographs were examined by Dr. J. L. A. Grout who reported that they showed a fine pin-point mottling all over both lung fields. Although generalized, the mottling was more intense at the mid-zones and towards the apices, with a nodular character similar to that seen in well-established cases of silicosis in the human being (Fig. 1). He also examined films obtained after intratracheal injections of a suspension of zircon (Fig. 2), and reported that the radiographs showed mottling in both lung fields, coarser than in the preceding films, and suggesting the coalescence of several of the affected areas. The morbid anatomy after injection of zircon was described in a previous paper (Harding, 1948). A radiograph of normal lungs is given for comparison (Fig. 3).

One rat died of bronchopneumonia, and a few of those that lived longest showed early bronchiectatic

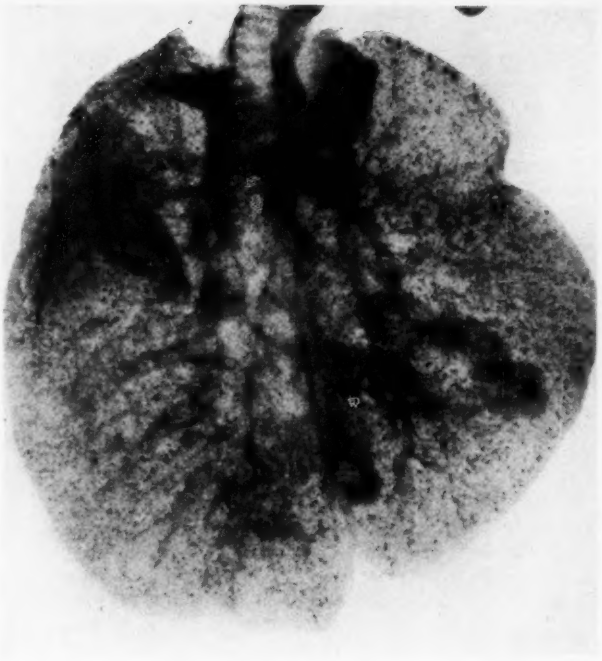


FIG. 1

FIG. 2

FIG 1..—Rat 542. Inhalation of zircon dust during seven and a half months : killed six months later Enlarged positive print of radiograph

FIG. 2.—Rat 104. Intratracheal injection of suspension of zircon on October 6, 1946 killed July 18, 1947, Enlarged positive print of radiograph

FIG. 3.—Normal rat. Enlarged positive print of radiograph.

FIG. 4.—Rat 542. See legend Fig. 1. Haematoxylin and eosin × 25.

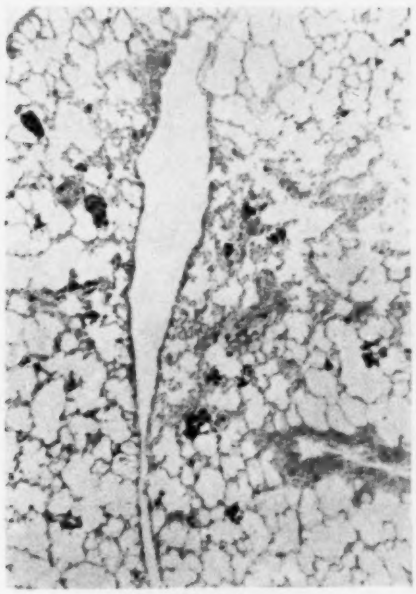


FIG. 4

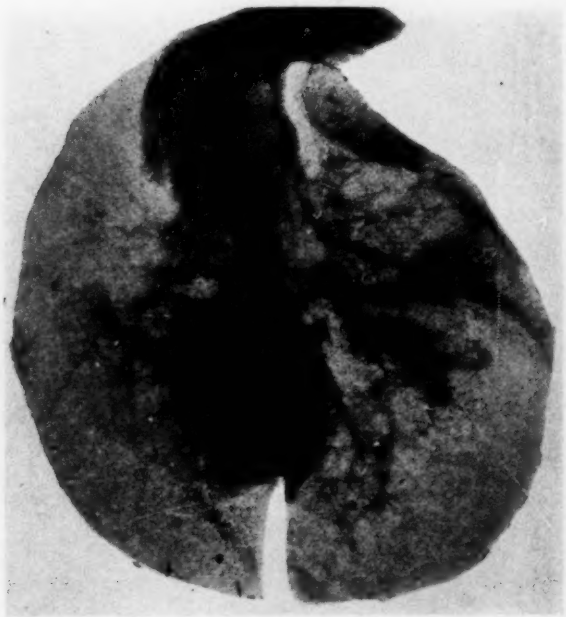


FIG. 3

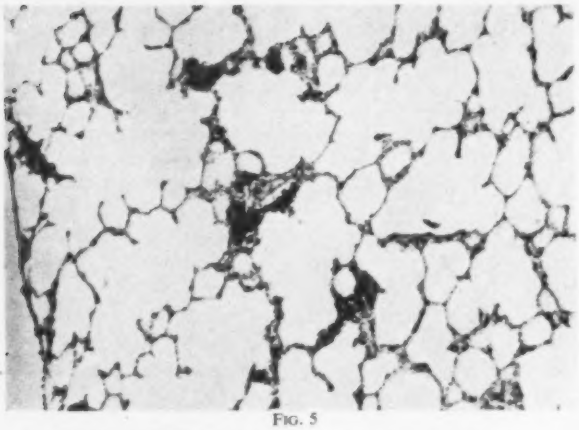


FIG. 5

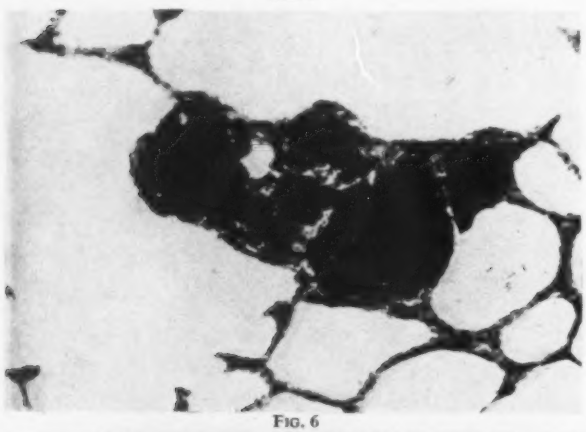


FIG. 6

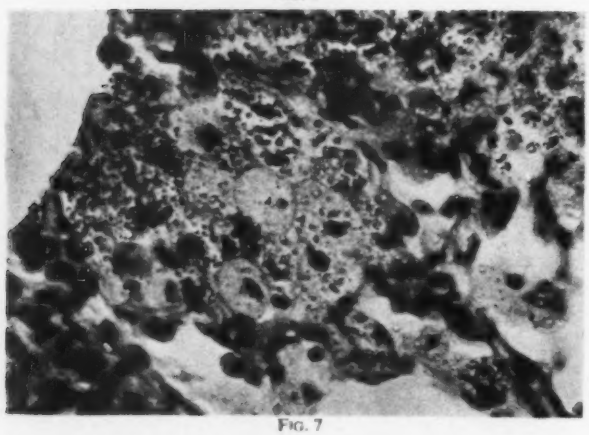


FIG. 7

FIG. 5.—Rat 537. Inhalation of zircon during seven and a half months : killed six months later. Haematoxylir and eosin × 65.

FIG. 6.—Rat 537. Haematoxylin and eosin × 190.

FIG. 7.—Rat 538. Inhalation of zircon during seven and a half months : killed six and a half months later. Haematoxylin and eosin × 500.

changes, which are found at a similar age in our stock rats : apart from these findings the lungs of all the animals were essentially similar. After fixation the lungs seemed slightly whiter and slightly more opaque than normal, but no abnormality was discernible on the cut surfaces. Microscopically small aggregates of cells densely packed with fine crystals were located at lymphatic junctions throughout the lungs, but most often just beyond the ends of the bronchioles or alongside small blood vessels (Figs. 4, 5). Pleural aggregates were rare, and the so-called " pleural drift " played no evident part in the localization. Around the dust-filled cells there were often a few cells that appeared to be small histiocytes, but the majority of the cells were so filled with crystals that no structural details could be seen (Fig. 6). In one or two areas the quantity of dust was much less, and it could then be seen that the cells were very large histiocytes (Fig. 7). No evidence of collagen formation could be found associated with these cellular aggregates, and we were unable to satisfy ourselves that there was any increase in reticulin fibrils. There was a suggestion of dilatation of alveoli in relation to the dust deposits but no genuine emphysema.

Discussion

Although we have not succeeded in getting very large quantities of zircon dust into the lungs of rats, the results show clearly that, like iron oxide (Harding, Grout, and Lloyd Davies, 1947), zircon can produce radiological shadows in these lungs in the complete absence of fibrosis. If zircon should come to be used at all extensively in industry, this is a fact of which radiologists should be aware.

From the evidence presented here and in a previous paper (Harding, 1948) it seems certain that zircon is harmless when inhaled by the rat or when a suspension is injected intratracheally, intravenously, or intraperitoneally into various laboratory animals. We have no explanation for the difficulty we found in getting appreciable quantities of zircon, as compared with other dusts, to reach and/or to be retained in the lungs of rats exposed to fairly high atmospheric concentrations : zircon powder is very heavy compared with most of the dusts with which we have had experience, but theoretical arguments are against mere " heaviness " of the particles playing a prominent role, and it seems unlikely that unusually efficient removal of particles can be responsible. Since we are unable to explain our findings, which might be due to some error in technique that we cannot trace, we do not wish to place much emphasis on them for the moment.

We realize that a failure to demonstrate any toxic reaction in animals, especially perhaps in rats, may

not be a sure indication of what may occur in man, in whom it seems likely that recurrent respiratory infections may increase greatly what would otherwise be very slight reactions to many dusts. Nevertheless, the complete absence of any reaction except phagocytosis is at least proof that zircon is much less dangerous than silica, for which it is proposed as a substitute in industry. If our findings that less zircon than several other dusts is retained in the lungs of rats when equivalent concentrations are breathed by them is confirmed, it would not imply that this would necessarily occur in man. If it were true it would be important, since, whatever the mechanism of production of damage in the lungs by various dusts, the extent of the damage will depend on the number of particles of appropriate size that are there present.

If these animal experiments are applicable to man, the replacement of silica by zircon wherever this is possible would reduce the risk of pneumoconiosis very considerably, both because zircon is less toxic, and possibly not toxic at all (Harding, 1948), and also because it is just possible that less of it might be inhaled into the lungs. Substitution of a safe material for a dangerous one is a basic method of prevention of industrial disease. The Foundries (Parting Materials) Special Regulations 1950 S.I. 1700 prohibit the use of silica as a parting powder : zircon is among the permitted substances so long as silica is not added to it. Zircon could, however, be substituted for silica in many other operations, e.g., in paints and washes, and even if its physical characters require the evolution of modifications of industrial techniques, the use of zircon appears to be one method, and on the basis of this note a profitable method, of eliminating silicosis. To condemn the use of zircon because methods and techniques for using silica are not immediately and totally applicable to it, would be wrong.

Summary

Dense radiological shadows are produced by aggregates of phagocytes containing zircon.

Apart from phagocytosis, and possibly slight small cell accumulation, there is no evident reaction to the presence of zircon in the lungs of rats.

Since zircon is far less toxic than silica (and possibly completely inert), and since animal experiments suggest that it is less readily inhaled into and/or retained in the lungs than the latter, it could provide a desirable substitute for silica.

We could not have proceeded without the help and advice of Dr. J. L. A. Grout, radiologist to the United Sheffield Hospitals. The photomicrographs were made by Mr. A. W. Collins, F.I.M.L.T., and the radiographs by Mr. A. L. Watson, M.S.R. The animals were cared for by Miss E. Wilkinson and Miss E. Parker.

The zircon used was given by Messrs. Colin Stewart Ltd., Winsford, Cheshire.

A small part of the expenses of this investigation was met by a grant from the Sheffield University Research Fund.

The dusting of the rats was done in the Research Department (Pharmacology Division) of Boots' Pure Drug Co., Ltd., Nottingham.

REFERENCES

Davies, T. A. Lloyd (1946). *British Journal of Industrial Medicine* 3, 111.
——, and Harding, H. E. (1949). *Ibid*, 6, 82.
Harding, H. E. (1948). *Ibid*., 5, 75.
——, Grout, J. L. A., and Davies, T. A. Lloyd (1947). *Ibid*, 4, 223.

Brit. J. industr. Med., 1952, **9**, 74

SKIN CANCER OF THE HAND AND FOREARM

BY

C. N. D. CRUICKSHANK and A. GOUREVITCH

From the Medical Research Council Industrial Medicine Research Unit, Birmingham Accident Hospital, United Birmingham Hospitals

(RECEIVED FOR PUBLICATION AUGUST 20, 1951)

A previous investigation (Cruickshank and Squire, 1950) demonstrated that a risk of skin cancer may occur in the engineering industry as a result of exposure to mineral oils. The conclusions were based upon the presence of hyperkeratoses observed upon the arms of machine operators, the biological testing of a commercial oil for tumour-producing activity, and a survey of the patients with scrotal cancer reporting to the United Birmingham Hospitals during the previous 10 years. The last part of this investigation yielded additional information concerning the natural history of scrotal cancer. It was decided to extend the enquiry by investigating cases of epithelioma of the hands and forearms which had reported to the same hospitals over a similar 10-year-period (1941–1950). Hands and forearms were selected as being also heavily exposed to any chemical carcinogens encountered during work. This investigation has yielded both clinical and aetiological information concerning skin cancer of the hands and forearms, and has enabled a comparison to be drawn between this condition and scrotal cancer.

Information was obtained from the Records Departments of the Queen Elizabeth and General Hospitals, Birmingham. The case records and histological reports of all patients treated for epithelioma of the hands and forearms were examined, patients were followed-up where possible, and if available the original sections were examined histologically in order to confirm the diagnosis.

Findings

During the 10-year-period under review 87 cases of cancer of the hands and forearms were found. Of these, 56 lived in the Birmingham area. The remainder had been referred to the United Birmingham Hospitals for treatment (mainly by the Radiotherapeutic Unit) from outside areas. The cases living outside Birmingham will not be considered further as they introduce an element of selection, and also because the follow-up proved to be unsatisfactory. Of the 56 Birmingham cases, 44 were male and the subsequent information refers only to these cases.

The main findings are set out in Table 1. This has been arranged exactly as in the investigation previously reported in order that comparisons may be easily drawn. The patients are classified in three categories according to the main agents encountered at their jobs.

It will be seen that of the 44, 18 gave a history of exposure to various oils, six to pitch, and 13 were in other occupations. In seven instances no information was available. Of the first group, 14 had been employed in the engineering industry. (This number includes one patient employed as a store keeper, and hence classified in Table 2 in Order XXIX.) The remaining four were a motor driver, a brickmaker, a slater and tyler, and a gold and silver polisher. The duration of exposure to oil varied from eight to 48 years, giving a mean of 28 years (S.E. = 4).

Since the numbers in each of the three categories in Table 1 might be attributed to the fact that the total population of Birmingham was exposed to these agents in the same proportion, the patients have been further grouped by occupation according to the Registrar-General's classification into 32 Orders (Table 2). Figures for the number of males over 14 years of age employed in these Orders in the Birmingham area are available from the Census Report (1931) and consequently incidence figures may be calculated. These figures can be regarded as only approximate since the number of cases is small and no correction for age distribution within the Orders is possible. The use of population figures from the 1931 census, however, is particularly justifiable in view of the long latent period and the long exposure required to initiate the disease.

The classification itself is not entirely satisfactory for the present purpose, as the Orders are very broad and may contain several categories with widely varying occupational hazards.

TABLE 1

ANALYSIS OF 44 MALE PATIENTS WITH CANCER OF HANDS AND FOREARMS ATTENDING UNITED BIRMINGHAM HOSPITALS 1941–50

Year Reporting	Main Exposure: Oil — Occupation	Oil — Glands Clinically Involved (G) or Not (O)	Oil — Age at Onset	Pitch, etc. — Occupation	Pitch, etc. — Glands Clinically Involved (G) or Not (O)	Pitch, etc. — Age at Onset	Other or Not Known — Occupation	Other or Not Known — Glands Clinically Involved (G) or Not (O)	Other or Not Known — Age at Onset
1941	—	—	—	—	—	—	*Horse driver**†	O	69
1942	Rolling mills	O	74	—	—	—	*Bricklayer's labourer**‡	G	58
	Fitter	O	56						
1943	Turner	G	76	*Gas worker**†	O	70	*Unknown**†	O	69
	Tool setter	O	42				Galvaniser :		
	*Fitter (Diesel oil)**	G	48				Acid, ammonia 7 yrs.	O	39
	Millwright's labourer	G	71				Dipping brass 18 yrs.		
							Bricklayer	O	67
							*Gardener**†	G	71
							Jobbing gardener	G	68
							*Unknown**	G	84
1944	Toolsmith 5 yrs.	O	68	—	—	—	Storekeeper (battery boxes and lead plates)	G	43
	Gear lapping 3 yrs.								
	*Stores (oil)**	O	79						
1945	Turner 3 yrs.	O	57	—	—	—	Unknown§	O	65
	Labourer (oil) 16 yrs.						*Unknown**†	G	71
	Motor driver 25 yrs.	G	41				Rubber worker§	O	42
	Machine operator 2 yrs.						Steel tube pickler§	O	33
1946	Tool setter	O	66	—	—	—	*Unknown**	G	42
							Groom 12 yrs.	O	67
							Lorry driver 33 yrs.		
							Unknown§	G	44
							Packing 29 yrs.	O	53
							Lorry driver 7 yrs.		
1947	Machine hand	G	70	—	—	—	Tap tester 1 yr.	O	79
	Drop forger	O	78				Viewing motor parts 22 yrs.		
1948	—	—	—	Plater (Gas Dept.)	O	58	—	—	—
				Stoker (gas)	O	80			
1949	Brickmaker	G	49	Tramway outside man (pitch ±, oil ±)	G	70	Unknown§	O	90
	Toolmaker	G	47				Sprayer 1 yr.	O	65
	Slater and tyler	O	46				Labourer (outdoor) 40 yrs.		
	Oiling 5 yrs.	O	55	Gas worker	O	44			
	Bricklaying 5 yrs.								
	Steel drawing 15 yrs.								
1950	Gold and silver polisher	G	60	Milam moulder	O	45	—	—	—

* (*italics*) Patient died by February, 1951.
† Cause of death apparently unrelated to carcinoma.
‡ Cause of death unknown.
§ Not established whether alive or dead by February, 1951.

TOTAL FINDINGS

Exposure	Patients	Deaths	Average Age
Oil	18 (12)*	2 (4)	60 (46)
Pitch	6 (13)	1 (4)	61 (58)
Other and doubtful ..	20 (9)	7 (1)	61 (61)
Grand total .	44 (34)	10 (9)	—

* The figures in brackets are the corresponding figures for scrotal cancer from Cruickshank and Squire (1950).

Table 2 shows that, of the 37 cases in which the occupation was known, 16 occurred in Order VII as compared with 21 in all other Orders. This figure is significantly high ($\chi^2 = 4{\cdot}3$, $P < 0{\cdot}05$).* Order VII which has the general title of "metal workers" is very large in this area, and although there are many

* In this and the subsequent χ^2 calculations on page 78, persons retired or not gainfully employed (Order XXXII) have not been included.

Brit. J. industr. Med., 1952, **9**, 74

SKIN CANCER OF THE HAND AND FOREARM

BY

C. N. D. CRUICKSHANK and A. GOUREVITCH

From the Medical Research Council Industrial Medicine Research Unit, Birmingham Accident Hospital, United Birmingham Hospitals

(RECEIVED FOR PUBLICATION AUGUST 20, 1951)

A previous investigation (Cruickshank and Squire, 1950) demonstrated that a risk of skin cancer may occur in the engineering industry as a result of exposure to mineral oils. The conclusions were based upon the presence of hyperkeratoses observed upon the arms of machine operators, the biological testing of a commercial oil for tumour-producing activity, and a survey of the patients with scrotal cancer reporting to the United Birmingham Hospitals during the previous 10 years. The last part of this investigation yielded additional information concerning the natural history of scrotal cancer. It was decided to extend the enquiry by investigating cases of epithelioma of the hands and forearms which had reported to the same hospitals over a similar 10-year-period (1941–1950). Hands and forearms were selected as being also heavily exposed to any chemical carcinogens encountered during work. This investigation has yielded both clinical and aetiological information concerning skin cancer of the hands and forearms, and has enabled a comparison to be drawn between this condition and scrotal cancer.

Information was obtained from the Records Departments of the Queen Elizabeth and General Hospitals, Birmingham. The case records and histological reports of all patients treated for epithelioma of the hands and forearms were examined, patients were followed-up where possible, and if available the original sections were examined histologically in order to confirm the diagnosis.

Findings

During the 10-year-period under review 87 cases of cancer of the hands and forearms were found. Of these, 56 lived in the Birmingham area. The remainder had been referred to the United Birmingham Hospitals for treatment (mainly by the Radiotherapeutic Unit) from outside areas. The cases living outside Birmingham will not be considered further as they introduce an element of selection, and also because the follow-up proved to be unsatisfactory. Of the 56 Birmingham cases, 44 were male and the subsequent information refers only to these cases.

The main findings are set out in Table 1. This has been arranged exactly as in the investigation previously reported in order that comparisons may be easily drawn. The patients are classified in three categories according to the main agents encountered at their jobs.

It will be seen that of the 44, 18 gave a history of exposure to various oils, six to pitch, and 13 were in other occupations. In seven instances no information was available. Of the first group, 14 had been employed in the engineering industry. (This number includes one patient employed as a store keeper, and hence classified in Table 2 in Order XXIX.) The remaining four were a motor driver, a brickmaker, a slater and tyler, and a gold and silver polisher. The duration of exposure to oil varied from eight to 48 years, giving a mean of 28 years (S.E. = 4).

Since the numbers in each of the three categories in Table 1 might be attributed to the fact that the total population of Birmingham was exposed to these agents in the same proportion, the patients have been further grouped by occupation according to the Registrar-General's classification into 32 Orders (Table 2). Figures for the number of males over 14 years of age employed in these Orders in the Birmingham area are available from the Census Report (1931) and consequently incidence figures may be calculated. These figures can be regarded as only approximate since the number of cases is small and no correction for age distribution within the Orders is possible. The use of population figures from the 1931 census, however, is particularly justifiable in view of the long latent period and the long exposure required to initiate the disease.

The classification itself is not entirely satisfactory for the present purpose, as the Orders are very broad and may contain several categories with widely varying occupational hazards.

TABLE 1

ANALYSIS OF 44 MALE PATIENTS WITH CANCER OF HANDS AND FOREARMS ATTENDING UNITED BIRMINGHAM HOSPITALS 1941–50

Year Reporting	Main Exposure: Oil — Occupation	Oil — Glands Clinically Involved (G) or Not (O)	Oil — Age at Onset	Pitch, etc. — Occupation	Pitch, etc. — Glands Clinically Involved (G) or Not (O)	Pitch, etc. — Age at Onset	Other or Not Known — Occupation	Other or Not Known — Glands Clinically Involved (G) or Not (O)	Other or Not Known — Age at Onset
1941	—	—	—	—	—	—	*Horse driver**†	O	69
1942	Rolling mills	O	74	—	—	—	*Bricklayer's labourer**‡	G	58
	Fitter	O	56						
1943	Turner	G	76	*Gas worker**†	O	70	*Unknown**†	O	69
	Tool setter	O	42				Galvaniser :		
	*Fitter (Diesel oil)**	G	48				Acid, ammonia 7 yrs.	O	39
	Millwright's labourer	G	71				Dipping brass 18 yrs.		
							Bricklayer	O	67
							*Gardener**†	G	71
							Jobbing gardener	G	68
							*Unknown**	G	84
1944	Toolsmith 5 yrs.	O	68	—	—	—	Storekeeper (battery boxes and lead plates)	G	43
	Gear lapping 3 yrs.								
	*Stores (oil)**	O	79						
1945	Turner 3 yrs.	O	57	—	—	—	Unknown§	O	65
	Labourer (oil) 16 yrs.						*Unknown**†	G	71
	Motor driver 25 yrs.	G	41				Rubber worker§	O	42
	Machine operator 2 yrs.						Steel tube pickler§	O	33
1946	Tool setter	O	66	—	—	—	*Unknown**	G	42
							Groom 12 yrs.	O	67
							Lorry driver 33 yrs.		
							Unknown§	G	44
							Packing 29 yrs.	O	53
							Lorry driver 7 yrs.		
1947	Machine hand	G	70	—	—	—	Tap tester 1 yr.	O	79
	Drop forger	O	78				Viewing motor parts 22 yrs.		
1948	—	—	—	Plater (Gas Dept.)	O	58	—	—	—
				Stoker (gas)	O	80			
1949	Brickmaker	G	49	Tramway outside man (pitch ±, oil ±)	G	70	Unknown§	O	90
	Toolmaker	G	47				Sprayer 1 yr.	O	65
	Slater and tyler	O	46				Labourer (outdoor) 40 yrs.		
	Oiling 5 yrs.	O	55	Gas worker	O	44			
	Bricklaying 5 yrs.								
	Steel drawing 15 yrs.								
1950	Gold and silver polisher	G	60	Milam moulder	O	45	—	—	—

* (*italics*) Patient died by February, 1951.
† Cause of death apparently unrelated to carcinoma.
‡ Cause of death unknown.
§ Not established whether alive or dead by February, 1951.

TOTAL FINDINGS

Exposure	Patients	Deaths	Average Age
Oil	18 (12)*	2 (4)	60 (46)
Pitch	6 (13)	1 (4)	61 (58)
Other and doubtful ..	20 (9)	7 (1)	61 (61)
Grand total .	44 (34)	10 (9)	—

* The figures in brackets are the corresponding figures for scrotal cancer from Cruickshank and Squire (1950).

Table 2 shows that, of the 37 cases in which the occupation was known, 16 occurred in Order VII as compared with 21 in all other Orders. This figure is significantly high ($\chi^2 = 4{\cdot}3$, $P < 0{\cdot}05$).* Order VII which has the general title of "metal workers" is very large in this area, and although there are many

* In this and the subsequent χ^2 calculations on page 78, persons retired or not gainfully employed (Order XXXII) have not been included.

TABLE 2

CLASSIFICATION BY OCCUPATION OF 37 MALE PATIENTS WITH HAND AND FOREARM CANCER

Order	Description	Nos. Employed in Birmingham (1931 Census)	Cases	Exposure of Cases		
				Oil	Pitch	Other
I	Fishermen	1	0 (0)*	—	—	—
II	Agricultural occupations	3,115	2 (0)	0 (0)	0 (0)	2 (0)
III	Mining and quarrying occupations	349	0 (0)	—	—	—
IV	Workers in the treatment of non-metalliferous mine and quarry products (includes gas workers)	481	4 (7)	0 (0)	4 (7)	0 (0)
V	Makers of bricks, pottery, and glass	1,615	1 (0)	1 (0)	0 (0)	0 (0)
VI	Workers in chemical processes; makers of paints, oils, etc.	752	0 (0)	—	—	—
VII	Metal workers (not electro plate or precious metals)	88,859	16 (14)	12 (11)	1 (0)	3 (3)
VIII	Workers in precious metals and electro plate	8,096	1 (0)	1 (0)	0 (0)	0 (0)
IX	Electrical apparatus makers and fitters (not elsewhere enumerated) and electricians	8,236	0 (0)	—	—	—
X	Makers of watches, clocks, and scientific instruments	768	0 (0)	—	—	—
XI	Workers in skins and leather, and makers of leather and leather substitute goods (not boots or shoes)	1,068	0 (0)	—	—	—
XII	Textile workers	267	0 (1)	— (1)	— (0)	— (0)
XIII	Makers of textile goods and articles of dress	3,473	0 (0)	—	—	—
XIV	Makers of foods, drinks, and tobacco	4,151	0 (1)	— (0)	— (0)	— (1)
XV	Workers in wood and furniture	17,301	0 (0)	—	—	—
XVI	Makers of and workers in paper and cardboard; bookbinders, etc.	685	0 (0)	—	—	—
XVII	Printers and photographers	3,858	0 (0)	—	—	—
XVIII	Builders, bricklayers, stone and slate workers; contractors	17,067	4 (0)	1 (0)	1 (0)	2 (0)
XIX	Painters and decorators	7,820	0 (1)	— (0)	— (1)	— (0)
XX	Workers in other materials	3,546	1 (2)	0 (0)	0 (2)	1 (0)
XXI	Workers in mixed or undefined materials (not elsewhere enumerated)	1,962	0 (0)	—	—	—
XXII	Persons employed in transport and communication	32,249	3 (1)	1 (0)	0 (1)	2 (0)
XXIII	Commercial, finance, and insurance occupations (excluding clerks)	37,187	0 (1)	— (0)	— (0)	— (1)

* Figures in brackets are the corresponding figures for scrotal cancer (see Cruickshank and Squire, 1950).

TABLE 2—*continued*

Order	Description	Nos. Employed in Birmingham (1931) Census)	Cases	Exposure of Cases		
				Oil	Pitch	Other
XXIV	Persons employed in public administration and defence (excluding professional men, clerical staff, and typists)	2,537	0 (1)	— (0)	— (0)	— (1)
XXV	Professional occupations (excluding clerical staff) ..	7,487	0 (0)	—	—	—
XXVI	Persons professionally engaged in entertainments and sport	2,155	0 (0)	—	—	—
XXVII	Persons engaged in personal service (including institutions, clubs, hotels, etc.)	9,046	0 (2)	— (0)	— (2)	— (0)
XXVIII	Clerks and draughtsmen ; typists	21,597	0 (0)	—	—	—
XXIX	Warehousemen, storekeepers, and packers	9,701	3 (1)	1 (0)	0 (0)	2 (1)
XXX	Stationary-engine drivers, dynamo and motor attendants	2,424	0 (0)	—	—	—
XXXI	Other and undefined	35,617	2 (2)	1 (0)	0 (0)	1 (2)
XXXII	Retired or not gainfully occupied	26,541	0 (0)	—	—	—
	Totals	360,011	37 (34)	18 (12)	6 (13)	13 (9)

* Figures in brackets are the corresponding figures for scrotal cancer (see Cruickshank and Squire, 1950).

different categories within the Order, many of the jobs involve exposure to mineral oils. Of our cases in Order VII, 12 were exposed to oil, one to pitch, and three to other agents. Clearly it is impossible in a study of this nature to provide unequivocal proof of the direct causal relationship between oil and cancer. Nevertheless the evidence cited above strongly suggests that exposure to oil is the likely cause of the increased incidence of cancer in metal workers.

In Table 1 is recorded the age of onset of the epithelioma, and the average age of those in each occupational category. There was no significant difference between the average ages of the three categories which were " oil " 60 years (S.E. mean = 3) ; " pitch etc." 61 years (S.E. mean = 7) ; and " other " 61 years (S.E. mean = 3). The average age of all groups was 61 years.

Of the 44 patients in this series, 10 were known to be dead by February, 1951 (the date by which the follow-up had been completed). In three instances it was impossible to confirm that the patient was still alive as the patient was not interviewed. However, of the 10 deaths only four could be attributed to the carcinoma ; in five, death was due to other causes, and in one case the cause of death was not established. Those patients dying from their cancer did so at the following intervals after first reporting : four months, six months, two years five months, and five years eight months. An approximate figure for the mortality due to cancer can therefore be estimated by omitting all patients who reported during the last two years of the period under review. (This also excludes the patient in whom the cause of death was unknown.) This gives 34 patients with four deaths or a case mortality of 12% (S.E. = 6%).

Table 1 also shows whether the patient had any clinical glandular enlargement (axillary or epitrochlear) at the time of first reporting. Of those patients who subsequently died, two had enlarged glands and two were recorded as developing them later. Of the remainder 16 had enlarged glands when they first reported. The fact that the glands were enlarged does not imply that they were secon-

dary to the cancer as a small proportion which were excised were diagnosed histologically as non-malignant.

Discussion

The main interest in these findings lies in a comparison between them and those concerning scrotal cancer previously reported (Cruickshank and Squire, 1950).

It will be seen that the minimum incidence of epithelioma of the hands and forearms among males in Birmingham is 44 per 10-year-period. The corresponding figure for scrotal cancer is 34. Provided that the patients reported with the same frequency the two conditions may be regarded as having approximately the same incidence. It is of interest, however, to compare the relative incidence of scrotal and hand and forearm cancer as reported by different workers. Henry (1947), working from notifications of industrial cancer, found that the site of election for oil cancer was the scrotum, the proportion being approximately 2 : 1. But his figures contained a large proportion of cases notified from the cotton industry. It is possible that the additional factor of the friction to the scrotum encountered during work and the relatively low degree of contamination of the hands and forearms may account for the difference. Smithers (1946) reports a preponderance of arm and hand cases over scrotal in the ratio of 3 : 1 in patients referred for radiotherapy. Jenkins (1948) and Winternitz (1947) both give a ratio of 2·5 : 1 for the relative incidence of upper limb and scrotal cancer in pitch and tar workers. In our two series it can be seen that the numbers attributable to pitch and tar in the hand and forearm group were less than in the scrotal group. There were more patients with hand and forearm than with scrotal cancer in the " oil " group, but the difference was not significant (Table 1).

In his analysis of deaths from skin cancer of all sites in England and Wales 1911–1945, Henry (1950) showed that the scrotum was the site of the growth in 7·9% and the upper limb in 6·1%. Clearly no comparison of the relative incidence of cancer in these sites is valid without reference to the nature of the population under consideration and the presumed causal agents.

Inspection of Table 2 shows that the cases of scrotal cancer tended to occur in the same Orders as did those of hand and forearm cancer. There were seven cases in Order IV and 14 in Order VII. Of the 14 patients with scrotal cancer in Order VII, 11 were workers who had been exposed to oil.

If the two series of patients are considered together it can be seen that 30 cases occurred in Order VII as compared with 41 in the rest of the population. This number is highly significant statistically ($\chi^2 = 8{\cdot}1$; $P < 0{\cdot}01$) although Order IV with a known high incidence of cancer is included with the " rest of the population ".

The increased incidence of cancer of these sites in metal workers is considered to be of importance, particularly as the extensive researches of Henry (1946, 1947, 1950) have failed to demonstrate any such increased incidence in this group. During the 30-year-period 1920–1949 Henry (1950) showed that only 46 cases of cancer of these sites were notified from the engineering industry. In this area only, during 10 years there were 23 cases in engineering which were notifiable as occurring in workers exposed to oils. Henry's analysis of deaths from scrotal cancer (1946) did not reveal an excessive mortality among metal workers. The number of deaths in our series is too small to allow of reasonable comparisons. It is possible, however, that the cancer risk in the engineering industry has not been long enough in existence for it to become apparent from mortality rates.

The average age of onset of the cancer in the hand and forearm series has been shown to be 61 years, while that in the scrotal series was 55 years. This difference is statistically not significant. Moreover there is no age difference between the three occupational groups in the present series in contrast with the scrotal series. The only important difference in the age of onset of the cancer in each of the three categories of the two series is the earlier onset of the cancer of the scrotum in oil workers. This shows a statistically significant difference from each of the other groups. The age of onset in our present series is less than that reported in a similar series by Johnson and Ackerman (1950), who found that the median age of 71 patients with carcinomata of the hand and forearm was 74 years.

The case mortality has been estimated at 12% while that from the scrotal cancer has been previously estimated at 38%. This difference, although suggestive, falls just short of statistical significance at the 5% level. Johnson and Ackerman (1950) report six deaths due to cancer out of 57 cases of hand and forearm cancer treated and followed-up for three years. This figure appears to be very close to our finding.

Conclusions

It has been demonstrated that a high proportion of epitheliomata of the hand and forearm as well as of the scrotum occur among workers exposed to recognized carcinogenic agents. Ryle demonstrated that persons of the lower income group (Class V, Registrar-General's Report) incurred an increased

incidence of skin cancer (Ryle, 1947). The work here reported confirms the findings of Henry (1946, 1947, 1950) that the type of occupation followed is a major factor affecting an individual's likelihood to develop cancer of the skin.

As a considerable proportion of these cancers may occur after the patient has retired from active work, the connexion between work and cancer is often not obvious. Nevertheless it is the responsibility of industrial medical officers and others concerned with occupational medicine to ensure that during the working life minimal exposure to known carcinogenic agents occurs, and that the statutory obligation to notify any cases which may arise is fulfilled.

Summary

An investigation of the patients treated for epithelioma of the hand and forearm at the United Birmingham Hospitals during the 10-year-period 1941–1950 has been undertaken.

The incidence and case mortality of epithelioma of the hand and forearm have been calculated and discussed.

A significantly large proportion occurs among "metal workers". Exposure to oil is suggested as the probable cause.

The findings are compared with those of a previous similar investigation of scrotal cancer.

We wish to thank the surgeons of the United Birmingham Hospitals who, through the chairman of the Medical Committee, Mr. B. T. Rose, F.R.C.S., gave permission to use their case notes; and Miss J. M. Levi, follow-up officer, United Birmingham Hospitals, for access to the very complete records in her care.

The majority of the histological sections and reports were prepared under the direction of the late Professor G. Haswell Wilson. We wish to express our indebtedness to Dr. J. G. Jackson who checked the diagnoses in such sections as were available. We also wish to acknowledge the continued interest and advice of Professor J. R. Squire, Leith Professor of Experimental Pathology, University of Birmingham.

References

Census of England and Wales (1931). Occupation Tables. H.M.S.O., London.
Cruickshank, C. N. D., and Squire, J. R. (1950). *British Journal of Industrial Medicine*, **7**, 1.
Henry, S. A. (1946). "Cancer of the Scrotum in Relation to Occupation." London.
——(1947). *Brit. med. Bull.*, **4**, 389.
——(1950). *Ann. roy. Coll. Surg. Engl.*, **7**, 425.
Jenkins, W. D. (1948). "Dermatoses among Gas and Tar Workers." Bristol.
Johnson, R. E., and Ackerman, L. V. (1950). *Cancer*, **3**, 657.
Ryle, J. A., and Russell, W. T. (1947). *Brit. med. J.*, **1**, 873.
Smithers, D. Waldron (1946). "The *X*-ray Treatment of Accessible Cancer." London.
Winternitz, J. G. (1947). *Brit. J. Radiol.*, **20**, 158.

Brit. J. industr. Med., 1952, **9**, 80.

SIMPLIFIED EYE-PIECE GRATICULE FOR ASSESSING THERMAL PRECIPITATOR DUST SAMPLES

BY

H. H. WATSON

From the Pneumoconiosis Research Unit of the Medical Research Council, Llandough Hospital, Nr. Cardiff

(RECEIVED FOR PUBLICATION JUNE 12, 1951)

Microscope counting and sizing of dust particles, for example, on thermal precipitator records, are done with the aid of an eye-piece graticule (Fig. 1), usually that designed by Patterson and Cawood (1936). Modifications have been made by Fairs (1943) and by May (1945) in which the sizes of the comparison circles increase by a constant factor of $\sqrt{2}$, but such graticules have not been used by many workers.

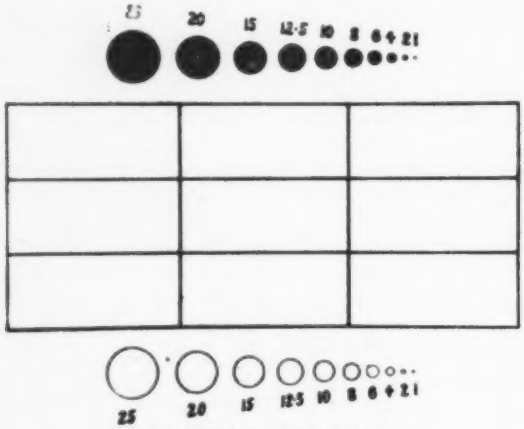


FIG. 1.—Patterson-Cawood graticule.

The Pneumoconiosis Research Unit, at the beginning of its dust assessment with the thermal precipitator, decided to use a particle number concentration within the restricted size-range of 0·5 to 5μ mean projected diameter as a measure of the hazardous fraction of air-borne coal-mine dust. Between 1947 and 1949 detailed size distributions were made with a Patterson-Cawood graticule, the cumulative size distributions being plotted on logarithmic probability paper. The percentage of particles within the restricted range was read off from the plot and the required number concentration determined. It also became our practice to quote particles per cubic centimetre (or percentages) within four size-groups

$$< 0{\cdot}5\mu,\ 0{\cdot}5 \text{ to } 2\mu,\ 2 \text{ to } 5\mu,\ > 5\mu$$

to give some indication of the fineness of the dust.

The information contained in the detailed sizing with the Patterson-Cawood graticule in 10 or more groups was rarely used, and, as the computing and graphical work required to produce the desired final result from the raw figures was considerable, a simplified procedure using a new three-spot graticule was developed. This graticule (Fig. 2) has been used in the eye-piece of an ordinary microscope and also on the screen of a Vickers projection microscope. It contains the conventional two rows of comparison circles, one row of open circles, and one row of black spots (filled-in circles), the individual circles being drawn with their diameters in the proportions of 5 : 2 : 0·5. In practice, by suitably altering the tube-length of the microscope, the magnification is adjusted so that when using a 2 mm. objective the circles correspond with diameters of 5μ, 2μ, and 0·5μ respectively.

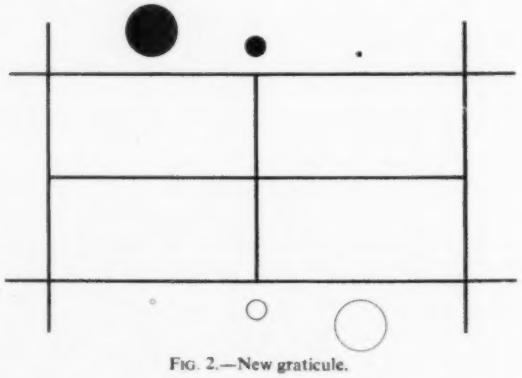


FIG. 2.—New graticule.

The graticule rectangle is 3·8 mm. long and 1·9 mm. wide, the diameter of the large circle being one-eighth of the length of the rectangle. The open circles are drawn so that the diameters to the outside of the lines are equal to the diameters of the respective black spots. Thus, when the largest circle is set to correspond with 5μ diameter, the length of the rectangle of the graticule is 40μ and its width 20μ. The short extensions of the rectangle lines have been found useful to guide the observer when a dust record is being traversed across the field of view.

The graticule has been used principally with Beck microscopes, the optical equipment of each consisting of a 2 mm. oil-immersion objective and a × 17 eye-piece. The working tube lengths of two such microscopes required to give the correct calibration are 162 mm. and 170 mm. respectively. It should be noted that the Beck × 17 eye-piece is of the positive type in which the focal plane is below the field lens. With a Huygenian type of eye-piece the focal plane lies between the field and the eye lenses, the relative magnifications of the two depending on the make. With this type it is more difficult to arrange a suitable size of graticule to ensure correct calibration ; generally a smaller size is required, one with long side of 3·1 mm. being a suitable compromise for a number of microscope combinations that have been tested, in which a × 10 or × 15 Huygenian eye-piece is used in combination with a 2 mm. (× 90) oil-immersion objective. A working tube length as much as 180 mm. appears to be permissible for counting and sizing particles larger than 0·5μ diameter ; visibility of particles closer to the limit of visibility will, however, be poor under this condition (Beadle and Patterson, 1939). In binocular microscopes in which the tube length is fixed, additional tube length may be obtained by inserting a collar of suitable length in each eye piece tube.

For use with the Vickers projection microscope the graticule is reproduced on the ground-glass viewing screen. Allowing for an overall magnification of × 2,000 (with a 2 mm. objective) the large circle is 1 cm. diameter. Line thicknesses are as follows :

Rectangle	0·02 in.
Open circles	0·006 in.

The lead-in or rectangle-extension lines are all 1 cm. long.

It was considered essential in designing a new graticule for dust assessment work to make it as simple as possible. Thus, in an earlier design the figures 5μ, 2μ, and 0·5μ were inscribed against the respective spots and circles, but these have been eliminated in the final design since they served no useful purpose.

When making a full size distribution with a Patterson-Cawood graticule it is necessary for the microscopist to be assisted by a recorder. The rate of counting (with recording) varies from observer to observer and with the type of dust deposit being assessed. Limits of counting rates for experienced microscopists vary from about one and a half to about three seconds per particle, with an average of about two seconds. With the three-spot graticule, when examination of the particles need not be so critical because of the wider size groups in which they are placed, the counting rate is usually about one second for each particle. With only four size groups in which to place particles it is a simple matter to use a key-board recorder. This practice is now standard, and it saves man power since the microscopist can himself record the count while looking down the microscope. The calculations necessary to produce the final result are few and simple, and no graphical work is needed resulting in a further saving of time compared with the old method.

TABLE 1

INCREASE IN PARTICLES CLASSIFIED IN FOUR SIZE GROUPS

Sample No.	Count (no sizing)	Count (with sizing)
1	95	109
2	99	115
3	93	100
4	67	76
5	83	94
6	201	214

Other simple modifications of the original Patterson-Cawood graticule to meet specific requirements might be suggested. For instance, in order to count the number of particles between two size limits, such as 0·5 and 5·0μ mean projected diameter, a two-spot graticule could be used. We have, however, continued to use the three-spot graticule, sorting particles into four size groups, in order to obtain some indication of the size distribution of the dust. There are indications that simple counting of the number of particles between two limits is not so accurate as when counting is done with some size classification. This is probably because the microscopist concentrates more if he has to classify each particle ; he will certainly count rather more

slowly and in doing so will be able to re-focus continually and to bring into view small particles that are out of focus when a large particle is being examined.

Table I illustrates that there is an increase in the total number of particles counted when they are classified in the four size groups. Traverses were made across thermal precipitator records first without sizing and then with sizing, using the three-spot graticule.

The graticule described in this paper is made by Messrs. Cooke, Troughton, and Simms and may be obtained on glass discs of either 18 mm. or 21 mm. diameter. It may also be obtained ruled on a ground-glass screen for use with the Vickers projection microscope.

REFERENCES

Beadle, D. G., and Patterson, H. S. (1939). *Nature, Lond.*, **144**, 327. See also comment by Ockenden, F. E. J., *Ibid.*, **144**, 516.
Fairs, G. Lowrie (1943). Chem. Ind. **62**, 374.
May, K. R. (1945). *J. sci. Instrum.*, **22**, 187.
Patterson, H. S., and Cawood, W. (1936). *Trans. Faraday Soc.*, **32**, 1084.

BOOK REVIEWS

The Application of Scientific Methods to Industrial and Service Medicine. By various authors. (Proceedings of a conference held from March 29th to March 31st, 1950.) Medical Research Council Report (1951). London: His Majesty's Stationery Office. 26 figs., 5 tables. Pp. 112. Price 3*s*.

Modern total war means that industrial health and Service efficiency are both at a premium. The two world wars, therefore, gave medicine with this slant a strong fillip. Psychology especially was stimulated, as exemplified by the work of Sir Arthur Hurst on hysteria in the first world war, and by that of Sir Frederic Bartlett and his Cambridge school of experimental, or physiological, psychology in the second. After the first war very much was forgotten, and the lessons taught then had to be learned all over again a generation later. It may be, however, that after the second war less will be forgotten and, as a suggestion that this is in fact so, comes this Medical Research Council " pink " publication which is the report of a conference held in the spring of 1950 when members of the main M.R.C. units, many of whom themselves worked in Service medicine during the war, met and described their work before an invited company.

In this type of medicine the physician is replaced by the statistician as the authoritarian father-figure, and in this report the general principles of conducting field surveys are presented by Professor Bradford Hill who enlivens them with characteristically amusing examples. The more seriously minded readers may feel here that the style is a little light for a scientific contribution to a symposium, but they will come to no harm if they keep in mind the adage that many a true word is spoken in jest. Professor Bradford Hill points out that careful thought must be given to when, why, and how a survey must be conducted. Not more than five unmistakably clear questions should be put to those who are being surveyed. Selection must be avoided, the sampling of the population must be truly random, and the results carefully controlled and clearly reported. Following this paper on principles, a number of other experts describe the use of the survey method for specific problems. Even if the main limitations of asking people questions are psychological, the statistician here shows clearly how to lessen them by careful conduct of the survey.

Fluorosis and beryllium poisoning are chosen to represent toxicological problems, and the interesting point is made that the early animal work with beryllium suggested that it was not poisonous.

In a section of the report on the improvement of human performance by laboratory studies it is shown that accidents increase when the temperature of the working environment rises too high or falls too low. Acclimatization to high temperatures means earlier sweating and more sweat is produced for each temperature increment. From the anthropometric point of view human performance can be improved if the dimensional range of men is known, because then machines can be made to fit them better, if the maker can be persuaded to take advice. Moreover, if the direction, amplitude, and force of movements are also known, then the functional fit will be better still. The accuracy, or otherwise, of this can be measured by the metabolic cost of the work, the frequency of accidents, or by the speed and accuracy of skilled performance. But Sir Frederic Bartlett points out that skill (which is replacing fatigue as a subject for discussion among psychologists) must be considered as a rhythmic whole, and not solely as a mosaic of easily detachable pieces. In doing a skilled task a psychological reflex arc is involved with its receptors and effectors, and whether it becomes fatigued or not depends upon the load, speed, and tolerance limits which are set. It is being confirmed experimentally that " intelligence " is much more a matter of knowing how to travel hopefully than of merely arriving at the right answer.

The last part of the report discusses the effect of dust on the lung, which is the most important pathological problem in occupational medicine today. Contributions by the members of the Pneumoconiosis Research Unit show clearly the difficulties of work in this field. For example, it has not yet been possible to produce a coal pneumoconiosis in animals although a wide range of them has been tried. Moreover, it is not yet known what it is in coal dust which scars the lungs of human beings, and silica is looking much less like the convenient scapegoat than it did. After discussing the variation between different observers in taking histories and in reading radiographs of the chest, the report ends by discussing the apparently simple but really difficult and fundamental question, " When is a man short of breath? "

In the field of pneumoconiosis, perhaps, the method of radiological categorization is being made to carry a load of more apparent precision than it is capable of doing. There is a debatable stage in every scientific observation where the normal shades imperceptibly into the abnormal. This is probably represented, in young men, by Category 1 of the chest radiograph classification method, but in many elderly men it is sometimes very difficult to say whether a film should be classed as 0, 1, or even 2.

It is clear from the report of this conference that industrial and Service medicine is much wider and more general than its classical clinical counterpart. About a

third of the report is taken up by the subject of field surveys, another third by fitting the machine to the man, about a fifth by pneumoconiosis, and a sixth by other kinds of toxicology. This balance fairly sets out the distribution of interests in industrial medicine at the present time, and the report is reasonably complete as a description of the activities of the main Medical Research Council units working in this field. Its sub-title might well be "Recent Advances in Industrial Health", but it lacks a section on accidents which represent an enormous wastage of human effort, especially in the heavy industries in general, and in the coal mining industry in particular.

Every research worker in the field under review can read the report, each section of which is written by an expert in his subject, with benefit, and merely dipping into it will tell industrial and Service doctors what original work is being done in their subject. On the other hand, the lay industrialist, the man who has to put into effect all that is prescribed therein, will probably not even read it at all. The problem of the distillation of recent research findings which can be applied to industry and their clear, even popular, presentation to the layman is more pressing than ever, and indeed it was underlined by a number of the speakers themselves in the reported discussions. A factory manager is a conservative man in a powerful executive position, and his first choice for bedside reading is not a government report. For him the pill must be sugar-coated, and presented in an attractive wrapping together with a persuasive list of the benefits which he may expect from swallowing it. R. C. BROWNE

Report of a Committee of Enquiry on Industrial Health Services. 1951. London: His Majesty's Stationery Office. Pp. 35. Price 1*s.* 3*d.*

A committee to examine the relationship between industrial health services and the other health services of the country was set up by the Prime Minister on June 1, 1949. Its terms of reference indicated that the major part of the investigation would be concerned with the distribution of medical manpower (defined as doctors, nurses, and auxiliary medical personnel) employed in all these services, and to what extent overlapping existed.

The Committee's report was presented by Mr. Attlee to the House of Commons on February 26, 1951, in the following terms (*Hansard*, Vol. 484, No. 59):

> "The Committee have found that, in general, doctors and nurses are well employed in the industrial health services without overlapping with the general health services; and they do not think that any developments of the industrial health services likely to take place in the immediate future will prejudice the general position in this respect.
>
> "The Report recommends that development of the industrial health services should be encouraged and properly co-ordinated with the general health services, and it makes recommendations for the establishment of co-ordinating machinery to that end. I should like particularly to invite the attention of employers to paragraphs 72 and 73 of the Report, which refer to the need for close collaboration with other organisations providing health services and for consultation with the appropriate Government Departments.
>
> "The Government accept the Report generally, subject to detailed consideration of the co-ordination machinery proposed. Accordingly although the need for the utmost economy in the use of medical manpower still persists, the suggestion I made on 1st June, 1949, that further development of industrial health services should be postponed for the time being, is to be regarded as no longer operative."

The Report describes the structure and function of the various sections of the national health service, and of the existing industrial health services, with reference to the manpower situation. It then discusses the possibility of overlapping in medical and nursing services generally, using for comparative purposes a summary of the functions of the industrial medical officer and the industrial nurse. The Committee found, for example, that there is overlapping where the industrial medical officer is not the Appointed Factory Doctor for statutory examinations of young persons. They "think" (and by using this word appear to avoid specific recommendation) that the industrial medical officer should, "in general" (whatever this means), be appointed to carry out these statutory examinations. A further section describes how doctors, nurses, and first-aid workers should be deployed in industry. The final part of the Report mentions steps to be taken by the Government and other parties concerned.

In view of the magnitude of its task the Committee can be commended on the relatively early appearance of its report, which in many places is informative to those without experience in industrial health services. The major recommendation is that a standing joint advisory committee should be set up by the Ministry of Health, the Ministry of Labour and National Service, and the Ministry of Fuel and Power to "co-ordinate the development of industrial health services." On this advisory committee would be representatives of employers, workers, doctors, and nurses, and the chairman would not be drawn from any government department. Judge Dale's Committee thus side-steps one vital and basic issue. What individual Ministry, if any, is to sponsor industrial health? There is little doubt that one good reason for the Prime Minister himself setting up the Committee, rather than one Minister or several Ministers jointly, was precisely the difficulty he or his advisers had in answering this question. By contrast, some seven years ago the Royal College of Physicians of London vigorously proposed that an industrial health service should be planned as an integral part of the national health service to come generally under the Ministry of Health. And the British Medical Association has specifically recommended that industrial health should come under that Ministry, using arguments difficult to refute. This Report says that "for the most beneficial development of the National Health Service, public health service, and industrial health services, the three must be co-ordinated". But there is no mention of how this could be done. It is perhaps kindest to think that the Committee felt such matters to be outside their terms of reference. But no doubt the point would eventually appear on the agenda for the proposed standing joint advisory committee.

It is now many months since the Report was published and accepted by the Government. It looks as if it were permanently on the shelf. Those who hoped for constructive proposals and a bold lead may well agree that this is the best place for it. DONALD STEWART

Physical Capacities and Job Placement. By Bert Hanman. 1951. Stockholm: Nordisk Rotogravyr. Pp. 167. Price 22 Swedish crowns.

This book, written by an industrial psychologist, summarizes the theory and practice of job placement in the United States of America and in nine European countries. The author's original idea was to assemble material on the placement of those workers commonly referred to as disabled workers, but this was changed to include all workers on the argument that "not more than one per cent. of all workers is physically fit for all work". In Hanman's view the great mass of the working population of the world is physically limited to some degree. The principles of placement outlined therefore apply to all workers alike.

The book is written for the most part in clear, concise, American language. The author's survey of present placement practices is informative and interesting. In discussing the problems of physical fitness in relation to work, however, Hanman is not on such familiar ground. But his arguments are stimulating. There is a prevailing view in the world that the disabled are different from other people, and that society is thus divided into superior and inferior beings. Disability so defined is that which is measurable from a medical point of view. If a person has detectable physical defects he is said to be physically impaired. If he has no defects he is thought to be physically fit. The truth really is that even so-called fit men are more often than not physically handicapped, and in both groups many individuals are not occupationally handicapped in the slightest degree. Their performance on the job provides adequate proof of this assumption.

Legislation requiring employers to "hire" disabled persons is condemned by Hanman. Our Disabled Persons (Employment) Act of 1944 comes in therefore for some lively comment. Legislation certifies the inferiority of disabled workers and they are thus branded sociologically. They may wear a distinguishing badge and from then on wear a black halo. This, of course, is not in accordance with the facts in Great Britain. Here the registration of disability is voluntary. There is no sociological branding even where badges are worn. The Disabled Persons Act is based on a desire to help a disabled man in practical ways rather than to give him tangible charity by way of money benefits. The Act is now an accepted part of our social system, it is non-political, and has placed Great Britain well in the lead in the matters of industrial rehabilitation and resettlement.

Hanman critically and skilfully examines two main methods of placement, the "disability" method and the "rating" method. The "disability" method classifies disabled people into convenient groups such as the one-armed or the one-legged. There is corresponding job classification after examination or analysis of the jobs themselves. The goal is the construction of a list showing the various disabilities that each job will tolerate. In theory this is simple but, in the author's view, fundamentally unsound. It disregards the extensive variation to be found in the physical and environmental demands of the same job being performed in different situations. It assumes that the physical capacities in any given group are similar. Hanman says: "This is an amazing error for medical men, since the individual nature of the ill and injured is a first principle in medicine". Finally this method is wrongly based on disability rather than on ability to do a job.

The "rating" method is based similarly on job and worker analysis, with the difference that for both purposes rating scales are applied, e.g. hard, moderate, light, very light; a, b, c, d; yes, no; 1, 2, 3, 4. In Hanman's view these terms are too general to be truly objective. There may be significant differences in the assessments of job analysts or doctors, and the results of assessments may hinder placement rather than assist it. The Pulheems system comes under this heading.

The author's main reason for writing his book is to describe his own solution to this problem through a new technique in job analysis. He has introduced what he calls a "specific" method for placement on physical grounds. Here the general terms used in rating scales are abandoned. A statement of facts is adopted and no attempt made therefore to rate facts according to a scale. By an ingenious method of using the hour as the standard unit it is possible, in Hanman's view, "to present the facts with a remarkable degree of accuracy". For example, from a study of the job demands analysis sheet the physician can immediately know that (in the analyst's opinion) his patient working on a given job would have to lift between 26 and 50 lb. for one hour out of eight worked; and that he would have to walk for three hours, and sit for one hour out of the eight-hour day. He then assesses his patient in terms of how many hours out of eight he can lift different weights, and how many hours out of eight would his physical condition allow him to walk without detriment to his health. Mechanical matching of man to job over a wide range of factors can then take place.

Hanman's arguments are based on extensive personal experience in the field of job analysis. He wisely states that his physical demands job analysis scheme is only one part of placement, and this immediately precludes considerable criticism. His next step surely must be to validate any claim that his methods should be generally accepted as an important part of placement. This can be done only by extensive investigation in collaboration with the medical profession. DONALD STEWART

First Aid—Medical and Surgical. By Cole and Puestow and 19 other Authors. 1951. U.S.A.: Appleton-Century Croft; 4th ed. Pp. 432. Price $4.

This book, largely a product of the Illinois College of Medicine, is described as being for the use of doctors, medical students, industrial surgeons, medical personnel of the Armed Forces, nurses, and first-aid attendants.

Whilst it is an easy book to read, it goes far beyond first aid as we understand it in England, and not only describes the work of the hospital casualty department, but even follows the patient into the operating theatre.

The book is written in clear and simple language, and is arranged in a familiar pattern. The first few chapters describe the functions and limitations of first aid. The general principles of the subject are enum-

erated, and a list is given of the material required. There are some surprising inclusions in this list, e.g. iodine, antitetanic serum, procaine, various surgical instruments, sulphadiazine and penicillin, to mention but a few. The chapters on anatomy, physiology, and bandaging are adequate and well illustrated.

In the treatment of wounds the use of sterile dressings is recommended, but if these are not available freshly ironed handkerchiefs or towels are suggested, an ingenious method of obtaining near sterility. Much mention is made of sulpha powders in this chapter, though later, in the text, it is recommended that they be given by mouth rather than dusted into the wound. The newer antibiotics are listed, including aureomycin and terramycin; the injection of 500,000 unit doses of penicillin are described as life-saving even in the first aid stage. Debridement of wounds is very inadequately described. Constrictive bandages are prescribed in the treatment of crush injuries of limbs, but little is made of the use of alkalis by mouth.

The chapter on the control of haemorrhage is clear and concise, and although it contains nothing new, it is one which could well be read by many first-aid attendants with advantage.

Fractures are dealt with in a workmanlike manner, and it is gratifying to see that the authors are not recommending the abandonment of splints in upper limb fractures. The principle of extension is well recognized, and the Murray-Jones splint for the arm and the Thomas splint for the leg are both described.

The chapter on gas and bomb casualties includes a chart giving a complete list of gases, their effects and treatment. This list could have been considerably simplified since many of these gases are now of academic interest only, and their inclusion only serves to confuse the student.

The second half of the book deals with emergencies, region by region, and each chapter includes a short note on the anatomy and physiology of the system involved. These are all quite straightforward.

Included in the closing chapters are medical emergencies, poisoning, a comparison of civilian and military casualties, a chapter on feet, and the last chapter of all, "First Aid in Industry". This last chapter is more concerned with the treatment which might be given in the medical department in a works rather than with first aid. It contains a summary of the conditions likely to be met with in industry, but does not make a serious attempt to describe treatment.

As occurs in books which try to encompass too wide a field for a variety of different readers, there is much which is unnecessary and likely to confuse the first-aid attendant who has both a limited knowledge and field. On the other hand, the information is inadequate for the surgeon or industrial medical officer.

R. A. TREVETHICK

THE OCTOBER (1951) ISSUE

The October (1951) issue contains the following papers :—

The Work of the International Labour Organization in Occupational Health. By A. Grut.

The World Health Organization and Occupational Health. By Sven Forssman.

The Bearing of Experimental Psychology upon Human Skilled Performance. By Sir Frederic Bartlett.

The Effects of BAL on the Metabolism of Lead and on the Symptomatology in Lead Intoxication. By E. C. Vigliani and N. Zurlo.

Some Observations on the Toxic Properties of 3 : 5-Dinitro-Ortho-Cresol. By V. H. Parker, J. M. Barnes and F. A. Denz.

Valeur de la Tomographie Pulmonaire dans l'Expertise de la Silicose. By L. Roche.

"Entente Radiologique." A Step Towards International Agreement on the Classification of Radiographs in Pneumoconiosis. By A. L. Cochrane, I. Davies, and C. M. Fletcher.

Pneumoconiosis in Boiler Scalers. By H. E. Harding and A. P. Massie.

The Hazards of Rope Making. By James A. Smiley.

An Appliance for the Prevention of Mercury Poisoning. By Franz Stocker.

Contribution à l'Etude de la Toxicologie du Trichloréthylène. By René Fabre and René Truhaut.

The Toxicity of Methylal. By Frank L. Weaver, Jr., Alan R. Hough, Benjamin Highman, and Lawrence T. Fairhall.

The Effect of Benzene and of Carbon Tetrachloride on the Concentration of Certain Vitamins, Fat, and Nitrogen in the Liver of the Rat. By Maurice E. Shils, Martin Sass, Margaret Wolke, Grace Marks, Leonard J. Goldwater, and Aaron Berg.

Plastic Splints and Appliances in Industrial Orthopaedics. By John T. Scales.

An Environmental Study of the Chromate Industry. By Monamy Buckell and D. G. Harvey.

Carcinoma of the Lung in Chromate Workers. By P. Lesley Bidstrup.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 7s. 6d.

ABSTRACTS

(This section of the JOURNAL *is published in collaboration with the two abstracting Journals,* Abstracts of World Medicine, *and* Abstracts of World Surgery, Obstetrics, and Gynaecology, *published by the British Medical Association. The abstracts are divided into the following sections : toxicology ; industrial physiology ; industrial lung disease ; industrial skin diseases ; accidents and orthopaedic surgery ; industrial ophthalmology ; environment ; general. Not all sections will necessarily be represented in any one issue)*

INDUSTRIAL TOXICOLOGY

Treatment of Lead Poisoning with Sodium Citrate. Report of Four Cases. HARDY, H. L., BISHOP, R. C., and MALOOF, C. C. (1951). *Arch. industr. Hyg. occup. Med.*, **3**, 267.

An account is given of 3 patients suffering from acute and 1 from chronic lead poisoning who were treated with sodium citrate. The 3 patients with acute disease suffered from abdominal pain and diarrhoea, and in one instance jaundice. The patient with the chronic disease had complained of abdominal pain and weakness over a period of 2 years. The patients were treated with sodium citrate in doses of 1 g. four times daily for a week, at the end of which time their symptoms were relieved. In one case the renal excretion of lead was suppressed, and in 3 cases there were prolonged urinary lead concentration and a slow rise of haemoglobin to normal levels, which the authors considered was evidence of the persistence of abnormal amounts of lead in these patients ; in the other case there was evidence that sodium citrate therapy hastened the excretion of lead.

The authors conclude that adequate oral doses of sodium citrate will control the symptoms of lead poisoning ; they do not agree that sodium citrate increases lead excretion. Increased coproporphyrinuria was found in all 4 cases, and to explain this the authors suggest that lead may act as a block between protoporphyrin and iron and prevent their normal combination in the formation of haemoglobin. It is possible that the neuritic pain, headache, encephalopathy, and colic present in plumbism may be explained by the coproporphyrins deposited in the tissues. It is possible that the finding of coproporphyrinuria may be a valuable aid in the prevention and early diagnosis of lead poisoning.

K. M. A. Perry.

A Syndrome of Radial Paralysis with Jaundice, and its Relation to Lead Intoxication. JIMÉNEZ DÍAZ, C., GILSANZ, V., LINAZASORO, J. M., and TAMAMES, C. (1951). *Rev. clin. esp.*, **40**, 163.

The authors describe a series of 10 patients who suffered from a syndrome of acute abdominal pain of a colicky type associated with jaundice and sudden onset of unilateral or bilateral paralysis of the upper limbs. Patients with slight paralysis showed the typical radial palsy with the escape of the supinator, but when the paralysis was severe then all the upper limb muscles were involved, and in 2 cases the lower limbs were also affected. All the patients were employed, or spent a great deal of time, in public houses or cafes, and the condition was caused by lead poisoning due to drinking mineral water with a high lead content. The differential diagnosis, clinical features, and pathology of the condition are discussed. Treatment includes the administration of Vitamins C and D and measures such as calcium injections and a diet rich in calcium to immobilize the lead, as its elimination is almost impossible.

René Mendez.

Bladder and Kidney Lesions in Dye-workers. MÜLLER, A. *Helv. chir. Acta*, **18**, 1. Bibliography.

Haemorrhage from the bladder and bladder tumours caused by occupational factors in the dye industry were first described by Rehn in 1895. Since then a considerable literature has accumulated, though, curiously enough, reports in this field from France have been few, despite the flourishing dye industry in that country. Some arsenic compounds were first under suspicion, but more recent views suggest that the anilines are associated with tumour formation ; also many other substances such as toluidine, xylidine, various naphthalines, Congo red, and fuchsin. The aetiological significance of many of these materials is still disputed, and confusion has been caused by the discovery that many dyestuffs are not pure substances but mixtures. Thus it is said that α-naphthylamine may contain from 5 to 10% of the beta product, which is the more harmful. Though some amino compounds are admittedly dangerous, others are not ; this radical cannot therefore be considered by itself.

It has been suggested that bladder disorders of the type described in man are essentially due to basic aromatic and primary amines. European workers all admit the harmful properties of β-naphthylamine and benzidine, though it is not universally accepted that similar properties are possessed by aniline and α-naphthylamine.

Recent experience of the Basle clinics suggest that not only amines, but also hydrocarbons such as anthracene, are harmful. It is known that tar and its derivatives may be carcinogenic, especially to the skin, but the literature contains isolated examples of other cancers from this cause, including those of the bladder. The prolonged inhalation of anthracene fumes, as occurred in the author's case, is rare. Though some absorption of the various carcinogenic substances may occur by other routes, the most important one is that through the lungs, by which both dust and fumes may

penetrate the body. It is known that the carcinogenic anthracene substances are eliminated through the urinary tract, and this is also the case with the amines mentioned. In many of the older factories considerable amounts of dyestuff escaped to the air as a fine dust, to which the workers were unavoidably exposed. Though the basic amino substances do no harm to the general body tissues, this appears to be due to their alteration in the tissues into harmless substances. Goldblatt regards the base itself as harmful, since such cancers are unknown in those handling phenol, acyl, or aryl derivatives of amines.

Apparently the noxious substances act on the mucosa of the urinary tract after excretion, and it is strange that no similar injuries occur in the lungs or alimentary tract. In man, who walks erect, most lesions are at the base of the bladder, while in experimental animals, as their gait would suggest, lesions tend to appear on the anterior wall of the organ. The lower incidence of lesions in the upper urinary tract is probably due to the more rapid passage of the irritant. Urinary stasis is also a factor, for as the *p*H rises the solubility of the amino bases falls. Some of these will come out of solution and be deposited on the floor of the bladder. Action through the blood stream in the urinary organs is also likely at times, so that the latter are exposed to double attack. Certain authors suggest that the first lesions are sub-epithelial, usually consisting in the development of new vessels. It is pointed out that, where tumours generally form, the vascular network round the bladder is richest. Circumscribed telangiectases and submucous suffusions are certainly seen in the early or pre-cancerous stages.

Many experienced workers dispute the haematogenous origin of the tumours. Whichever theory is accepted, the development of tumours many years after exposure to the irritant ceases is not easily explained. In animal experiments traces of certain dyes have been found in the bladder years after their administration.

Statistical proof of the frequency of these lesions in dye workers is not easily obtained, but it is certain that greater manufacturing precautions have diminished their incidence. In the Basle district death from this disease does not occur much earlier in dye workers than in its other victims. The author finds the average period of exposure before lesions develop to be just under 12 years, in a range between 36 and 6 years. Cancer is rare in those with acute poisoning. Acute poisoning may cause extensive but transient irritative lesions which rarely pass into a chronic stage of inflammation. Haemorrhage is an early symptom of cancerous change, but, though this was previously denied, tumours may form without the discovery of occult blood in the urine. Dysuria is common, but many symptoms are often absent until the neck of the bladder is involved or ulceration and incrustation have developed. During the latent period which is common to all tumours no symptoms at all may occur.

Diagnosis rests on early cystoscopy, an examination which should never be omitted. It may be very difficult to find the smaller tumours. Instillation of adrenaline will check bleeding and thus facilitate investigation. Diagnostic partial excision may stimulate spread. There is some suggestion that a familial tendency to carcinoma is indicated in certain cases. Benign tumours account for about a quarter of those seen in the dye industry, but these may develop cancerous changes. Simon maintains that aniline tumours have a more favourable clinical course than those of unknown aetiology. In Basle multiple primary tumours of the bladder were recorded in 10 cases, and in some of these cases other organs were affected and other types of cancer occurred.

The Basle school employs conventional treatment of the disease and recommends drastic measures to lessen exposure to the noxious agents. Prophylaxis is incomplete if regular examination of the workers is neglected; this should include cystoscopy.

G. C. Pether.

The Character and Distribution of Disease in American Industries Using Beryllium Compounds. HARDY, H. L. (1951). *Proc. roy. Soc. Med.*, **44**, 257.

Beryllium poisoning appears in acute, subacute, and chronic forms. In the first there may be contact dermatitis, conjunctivitis, or respiratory disease (with dyspnoea, cyanosis, weight loss, and *x*-ray changes which may take a year to clear). A few patients have died of pulmonary oedema. In the subacute form there are fine, nodular shadows in the lung fields on radiography, with some disability.

Chronic beryllium poisoning, sometimes called delayed pneumonitis, may occur as a result of remarkably slight exposures to beryllium. Symptoms sometimes occur immediately afterwards, but usually are delayed from weeks to several years. New cases are still occurring, and the maximum time lag is not yet known. Often there is a precipitating event such as a pregnancy or infection. Weight loss is the rule, and it may be very severe; there are also asthenia, dyspnoea, cough, gastro-intestinal disorder, and sometimes hyperpyrexia. There is generalized granulomatous involvement of the lungs and liver, and beryllium can be found in these tissues. In some cases there is hypercalcaemia and formation of renal calculi. The prognosis is poor, with remissions and exacerbations; the mortality is 20%, and in those who survive disability is serious. A small minority are asymptomatic. Sometimes chronic disease follows on one or more attacks of acute disease. There is often impairment of liver function, and the serum protein level and calcium-phosphorus metabolism may be abnormal. Diagnosis depends on the demonstration of exposure to beryllium, and is assisted by spectrographic analysis of body fluids or tissues. The only effective treatment is conservative, using oxygen; ACTH has been tried.

In most cases beryllium oxide is the aetiological agent, and the bizarre incidence of cases may be accounted for by varying physical characteristics of particles. Beryllium poisoning appears to be a systemic disease, with formation of granulomata in various organs and with irreversible fibrosis following later. The element has a direct toxic action on certain enzyme systems. The author suggests that beryllium is stored harmlessly if absorbed slowly, but may be mobilized and become toxic during other disorders. [The pattern of beryllium

poisoning in U.S.A. has not appreciably altered since the same author first described 17 chronic cases in 1946. More than 180 such cases have now occurred.]

J. N. Agate.

Hydrogen Sulfide Poisoning in Shale Oil Industry. AHLBORG, G. (1951). *Arch. industr. Hyg. occup. Med.*, **3**, 247.

Sweden's isolation during the war made it necessary to extend the production of shale oil. In this industry there was considerable exposure to hydrogen sulphide owing to the high concentration of sulphur in the shale layers. Estimation of the air at various places in the workings showed that the concentration of hydrogen sulphide was more than 0·060% in 9 places, more than 0·015% in 11 places, more than 0·002% in 24 places, and less than 0·002% in 62 places. This figure of 0·002% is considered to indicate the maximum concentration allowable for prolonged exposure to the gas.

During the period from 1943 to 1946, 59 cases of acute gas poisoning with unconsciousness occurred at the shale-oil plant, but there were no deaths. The symptoms were a sudden feeling of fatigue, especially in the legs, dizziness, and intense anxiety, followed by unconsciousness with or without respiratory failure. After recovering consciousness the patients complained of pronounced pain in the back of the head, dizziness, and sometimes nausea. The only objective symptoms found on examination were nystagmus and Romberg's sign. In 6 cases there were further sequelae, of which damage to the ear affecting equilibrium was the most prominent. There were also changes of temperament and neurasthenic symptoms, recovery from which took about 2 months, and there was considerable sensitivity to the gas afterwards. Subacute poisoning was characterized by kerato-conjunctivitis and irritation of other mucous membranes ; no permanent damage to the eyes occurred. There is no positive evidence of chronic hydrogen sulphide poisoning, but the frequency of neurasthenic symptoms increased with the degree of hydrogen sulphide exposure and the length of employment.

K. M. A. Perry.

Potassium Bromate Poisoning. PARKER, W. A., and BARR, J. R. (1951). *Brit. med. J.*, **1**, 1363.

Potassium bromate is used as a neutralizer in home permanent-wave outfits. Although poisoning due to this substance has been recorded only twice, similar cases may be expected in view of the popularity of these permanent-wave outfits. No bromide or bromine is liberated from potassium bromate on incubation with normal gastric juice at 38° C. for 3 days. Previous workers have described among the toxic effects of bromates vomiting, diarrhoea, depression of the nervous system (particularly the respiratory centre), and gross tubular degeneration of the kidneys.

A 3-year-old boy drank a quarter of the clear fluid contained in a milk-bottle, which contained ½ oz. (14·2 g.) of potassium bromate dissolved in 1 pint (570 ml.) of water. One hour later he complained of nausea, vomited several times, passed 2 fluid stools, and had much abdominal discomfort. Retching started later followed by haematemesis estimated at "half a cupful". Six hours after swallowing the fluid he was admitted to hospital unconscious, pale, and flaccid. The pupils reacted to light but the tendon reflexes were absent, the pulse was 100, and the blood pressure 85/45 mm. Hg. Eyeball tension was diminished, and the tongue was dry although the skin was moist. The respirations were 30 per minute, shallow, and the breath smelled of acetone. The axillary temperature was 97° F. (36·1° C.).

Gastric lavage was performed and 30 oz. (850 ml.) of 5% dextrose given by intravenous drip. Two hours later the pulse was 160 and the blood pressure 110/65 mm. Hg (normal pulse and blood pressure at this age are 105 and 80/60 mm. respectively). Consciousness was regained 3 hours after admission. Intermittent vomiting occurred in the next 3 days. The child was irritable, pale, and motionless. Anuria was present for 24 hours, increasing amounts of urine being passed in the next 2 days. Albumin was present in the urine for 7 days—at first 6 g. per litre. No other abnormal constituents were present except acetone on the second day. The child took an active interest in his surroundings on the seventh day, convalescence was uneventful, and review at intervals during the next month revealed no abnormality, though the mother said he was fretful and irritable.

R. Hodgkinson.

Cadmium Poisoning. COTTER, L. H., and COTTER, B. H. (1951). *Arch. industr. Hyg. occup. Med.*, **3**, 495.

Acute cadmium poisoning is usually manifested by symptoms of respiratory irritation which are severe and often fatal. This paper describes the cases of 5 men, all of whom recovered after illnesses which were more or less mild, and indeed might not be recognized as cadmium poisoning. Short clinical histories are given, together with details of all the biochemical and haematological findings.

All the men were exposed to cadmium fumes or dust, two being metal-burners and 3 being engaged in mixing powders. The 2 metal-burners suffered an acute illness following a single instance of exposure to cadmium. The first developed severe headache and later coma, but recovered consciousness in a short time ; his other symptoms disappeared in 3 months. The cadmium content of the blood was 0·18 mg. per 100 g. initially, and this fell to 0·12 mg. per 100 g. after 3 months, but rose again 0·14 mg. per 100 g. when the patient had a respiratory infection a year later. When this infection subsided, cadmium disappeared from the blood. The second metal-burner developed headache, dizziness, weakness, and pain in the legs after encountering some plated metal in his work. His blood cadmium was 0·12 mg. per 100 g., but after 5 months only a trace was found, and by this time his symptoms had subsided. The third case was that of a man who had worked with coloured powders for 3 years, and had felt tired for some time. Both lead and cadmium were found in the blood and urine, but 6 months after he was removed from exposure he felt well and neither metal was detected biochemically. The fourth victim had been powdering cadmium sulphide for a year without wearing a mask, and developed cough, dyspnoea,

and jaundice. The chest signs cleared up after 3 days, and the jaundice disappeared in a week. The blood cadmium value was 0·38 mg. per 100 g., but this dropped to *nil* in 3 months. [The patient is said to have been exposed to lead, but no evidence of this is presented.] The fifth patient developed nausea, abdominal pain, and lassitude after handling powdered cadmium compounds for a year. His liver was "felt well below the costal margin".

From the laboratory findings it was concluded that in all the cases there was evidence of liver damage and anaemia, while in the third, fourth, and fifth cases there was renal injury in addition. These abnormalities all returned to normal in a few months.

[The evidence of liver damage is highly equivocal and the figures in the original paper should be consulted.]

W. K. S. Moore.

The Value and Mode of Action of Sodium Tetrathionate as an Antidote in Cyanide Poisoning. BINET, L., WELLERS, G., and DUBRISAY, J. (1951). *Pr. méd.*, **59**, 641.

In cyanide poisoning many sulphur-containing substances have a remedial effect, and it is known that cyanides are elminated by the body in the form of thiosulphates. Among the substances whose detoxicating effect has been investigated are colloidal sulphur, cystine and cysteine, reduced glutathione, and sodium hyposulphite. The authors consider that materials with an oxidized component are more effective than those containing reduced sulphur. With these considerations in mind they directed special attention to sodium tetrathionate. All experiments were made with adult rats, and the minimum lethal dose (MLD) was determined; this was found to be 15 mg. per kg. of body weight and caused death in from 10 to 45 minutes.

In assaying the antidote, varying amounts of cyanide were given subcutaneously and the tetrathionate was always injected intraperitoneally at the moment when the animal lay on its side and made no further movement; this preceded the stage of convulsions. In from 1 to 5 minutes after administration the animals got up and in a few moments behaved normally. This happened when 1 or 2 MLD had been given, was less dramatic after 3, and failed entirely after 4 MLD when, even if twice the amount of antidote was given, two-thirds of the rats died. The antitoxic action of the tetrathionate is not strictly proportional to the amount given, and this seems to invalidate the theory of a direct action on the cyanide *in vivo*.

Experiments showed that hyposulphite was no more effective in cyanide poisoning, weight for weight, than the tetrathionate. In fact, when four times the MLD was given, the latter remedy was more effective, since one-third of the animals survived, but hyposulphite did not save any. When lesser amounts of cyanide than 4 MLD were used, recovery with tetrathionate was more marked and rapid than when hyposulphite was used.

It occurred to the authors that the action of tetrathionate differed fundamentally from that of hyposulphite and might be exercised through the intermediary of glutathione, which it reduces *in vivo*. Cyanide also acts on it *in vitro*, and the higher the amount of oxidized glutathione in the tissues, the better can the animals tolerate cyanide poisoning. But this tolerance to the poison must depend on the amount of glutathione available, and this explains the inability to tolerate more than thrice the fatal dose. Experiments were made to investigate this hypothesis. Tetrathionate was given intraperitoneally before cyanide was injected subcutaneously; the protective value of the former was greatest when from 15 to 20 minutes elapsed between the injections. Most of the animals, including those which recovered, showed no sign of disturbance for the first 5 minutes, but were nevertheless distressed for 10 minutes subsequently.

It was found that the state of oxidation of glutathione varied from time to time, a rise being followed by a fall and then by a further rise. This explains the phenomena described, for the concentration of cyanide also has variations; hence the intervals between the appearance of the various symptoms of poisoning.

Further experiments supported the general thesis that there is a first stage, 5 to 10 minutes after the injection of tetrathionate, in which glutathione is oxidized by the former and acts on the cyanide in the blood. In a second stage these changes take place in the tissues and principal organs, such as the liver, kidneys, and muscles.

G. C. Pether.

A Toxicological Study of Some Polypropylene (Polyoxypropylene) Glycols. SHAFER, C. B., CARPENTER, C. P., CRITCHFIELD, F. H., NAIR, J. H., and FRANKE, F. R. (1951). *Arch. industr. Hyg. occup. Med.*, **3**, 448.

Polypropylene glycols are used industrially as hydraulic-fluid bases and plasticizers. Chemically they are polymers of propylene oxide, which itself possesses little pharmacological activity. On the other hand, the polypropylene glycols possess considerable pharmacological activity, particularly in the lower molecular-weight ranges.

Three polypropylene glycol mixtures were investigated with average molecular weights of 425, 1025, and 2025. The acute toxicities (LD50) of these mixtures for rats were determined and were found to be, respectively, 2·91 g., 2·15 g., and 9·76 g. per kg. when given by mouth; 0·46 g., 0·23 g., and 4·47 g. per kg. when injected into the peritoneal cavity; 0·41 g., 0·12 g., and 0·71 g. per kg. when injected intravenously. Thus polypropylene glycol 1025 proved to be the most toxic of the three, while additional determinations for dipropylene glycol showed that it was much less toxic than any of the polymeric mixtures.

None of the mixtures showed any deleterious action on the skin or in the eyes of rabbits, and only polypropylene glycol 425 was absorbed through the skin in sufficient amount to produce toxic signs; inhalation experiments with rats showed that polypropylene glycol 425 was moderately toxic, while the other two mixtures were comparatively innocuous.

The toxic manifestations after oral administration to rats included sluggishness, prostration, tremors, and convulsions. Intraperitoneal injection led to narcosis, frothing at the mouth, and tremors, while audible rales

occurred before death. The findings after intravenous injection were similar, but, in addition, convulsions were caused by polypropylene glycols 1025 and 2025. The pathological findings were generally of congestion in the various organs, but the kidneys were ischaemic.

The action of these polypropylene glycols on the heart was investigated, and only polypropylene glycol 425 was found to have any effect. The most notable change was the occurrence of ventricular ectopic beats. Finally, the effect of the polypropylene glycols on various isolated enzyme systems from brain tissue was investigated. All three mixtures exerted an inhibitory influence on the oxidative phase of glycolysis. *W. K. S. Moore.*

Protection Against Experimental Beryllium Poisoning by Aurin Tricarboxylic Acid. WHITE, M. R., FINKEL, A. J., and SCHUBERT, J. (1951). *J. Pharmacol.*, **102,** 88.

INDUSTRIAL LUNG DISEASE

Renal Function in Silicosis. SAITA, G., and ZAVAGLIA, O. (1951). *Med. d. Lavoro,* **42,** 41.

The authors studied the renal function of 20 patients aged 36 to 59 years who had silicosis. Patients with cardiac disease, hypertension, and other serious disease, or with a history of renal disease, were excluded from the series. Six of the patients included had active pulmonary tuberculosis with positive sputum. Albuminuria was found in 4 cases, lipoiduria in 20, reduced ability to excrete dilute urine in 10, and a slight rise in blood urea level in 8. The authors discuss 3 possible mechanisms to account for the changes in renal function : the co-existence with silicosis of cardiac insufficiency, the elimination of silica through the kidneys, and the damaging effect of free silica on the mesenchymal tissues. They quote histological studies said to demonstrate fibrotic changes in the spleen, liver, and kidneys in patients dying from silicosis, and conclude that it is these effects which are responsible for the changes in renal function. *John Pemberton.*

Pneumoconiosis and Silicosis. VIGDORCHIK, N. A. (1951). *Gigiena,* No. 1, 20.

Quartz dust (SiO_2) produces diffuse or localized fibrosis of the lung tissue. It is still doubtful whether any dusts other than quartz can produce a similar fibrosis. In other words, are there, except for silicosis, any other forms of pneumoconiosis ? The term pneumoconiosis is still not defined properly and this causes a lot of misunderstanding. For instance, Tibbs defines pneumoconiosis as " any morbid condition of the lungs caused by inhalation of dust ". According to that terminology one must call a bronchitis, asthma, or bronchiolitis, which may be caused by dust, also a pneumoconiosis.

The author then proceeds to present evidence proving that dust which does not contain quartz affects the respiratory tract only as far down as the alveoli, and that the quartz dust, in addition to the above, can also produce a diffuse fibrosis in the perialveolar tissue—that is, in the connective tissue and the lymphatic network forming the stroma of the lung.

H. W. Swann.

INDUSTRIAL SKIN DISEASE

The Occurrence of Asthma and Eczema in Workers Engaged in the Production of Hydrogen Peroxide. BARSOTTI, M., PARMEGGIANI, L., and SASSI, C. (1951). *Med. d. Lavoro,* **42,** 49

The authors describe the manufacture of hydrogen peroxide, involving exposure of the workers to ammonium sulphate. Eczema occurred in 27·4% of 106 men engaged in production compared with an incidence of 7·5% among 207 labourers and 0·7% in 277 workers in a factory producing tartrates. The eczema first affected the interdigital clefts of the hands and flexor surfaces of the forearms, and was active in 17% and quiescent in 10·4%. It came on in most cases within 3 months of starting work and relapses were frequent after return to work. Patch tests were negative for potassium sulphate, sulphuric acid, and hydrogen peroxide, to which the workers were also exposed, but positive in 32 out of 46 cases tested with ammonium sulphate. It was also found that 12·2% of the production workers suffered from bronchial asthma compared with 4·3% in each of the other two groups of workers. Preventive measures are recommended. *John Pemberton.*

Experimental Beryllium Granulomas of the Skin. DUTRA, F. R. (1951). *Arch. industr. Hyg. occup. Med.,* **3,** 81.

Pulmonary and skin granulomata occur in men exposed to certain beryllium compounds. An attempt was made to produce such lesions by implanting into skin samples of beryllium metal, two kinds of beryllium oxide calcined under different conditions, and two kinds of fluorescent powder containing beryllium oxide, of identical chemical composition but calcined differently. In rabbits and rats no lesions developed. The skin of pigs more nearly resembles that of man : the powder was therefore implanted into pigs' skin, together with various control implants, and biopsies were taken at intervals from 2 days to 6 months. The initial wounds healed spontaneously. Tissue reactions occurred in the subcutaneous fat immediately below the dermis. Beryllium metal and the two oxide samples produced foreign body reactions of non-specific granulomatous type. The two fluorescent powders produced the typical whorled, collagenous granulomata seen in human berylliosis. The powder calcined for a shorter time at lower temperature gave the more extensive and prolonged reaction. This may have been due to increased solubility of beryllium oxide and to the higher surface : weight ratio of its particles. *J. N. Agate.*

Osteogenic Sarcoma after Inhalation of Beryllium Oxide. DUTRA, F. R., LARGENT, E. J., and ROTH, J. L. (1951). *Arch. Path. Chicago.,* **51,** 473.

ENVIRONMENT

Physiological and Clinical Observations at High Altitudes. OUDOT, J. (1951). *Pr. méd.*, **59**, 297.

Tests were carried out on 8 subjects in the course of a Himalaya expedition in 1950. Observations were made between 2,500 and 5,900 metres, and further observations were later made on the same subjects in Paris, concerning the cardiovascular system, respiratory system, and metabolism, while a few observations were made on the central nervous system and blood (haemoglobin). Investigations were of necessity confined to simple clinical tests and estimations of basal metabolic rate. The results are tabulated. *T. C. D. Whiteside.*

The Effect of Oxygen Inhalation at High Altitudes. OUDOT, J. (1951). *Pr. med.*, **59**, 326.

In continuation of the above report, the action of oxygen on resting pulse, blood pressure, and respiration, and the effects of oxygen given during exertion, are examined. The author discusses the relative merits, on a high altitude mountain climb, of giving oxygen either at rest, so as to aid recovery, or during exertion. *T. C. D. Whiteside.*

The Relation of Circulatory Rate to Aeroembolism and Aeroemphysema. WEDRAL, J. W., and IVY, A. C. (1951). *J. Aviat. Med.*, **22**, 13.

The authors sought a method of producing gas bubbles in the periarticular tissues of dogs exposed to simulated high altitude, with a view to clarifying the problem whether the periarticular bubbles demonstrable radiographically in man are intra- or extra-vascular, and, secondly, to test the validity of the concept that the relative resistance of small animals to the effects of decompression is dependent on circulatory factors.

The dogs were taken to altitudes of 40,000 to 50,000 feet (12,190 to 12,540 metres) and were given oxygen at the ambient pressure : radiographs of the thighs and legs were taken at altitude, and a dissection of the tissues was made forthwith. It was found that gas in the veins and arteries, periarticularly, and in the intermuscular fascial planes can be recognized radiographically if the amount is sufficient. In anaesthetized dogs which died after reaching 48,000 feet (12,760 metres), the presence of gas in the veins, in the fascial planes of the thigh, and around the knee-joint was established by *x*-ray examination and dissection. In anaesthetized dogs resting at altitudes of 40,000 to 48,000 feet (12,190 to 12,760 metres) bubbles were not detected by either technique. Exercise of one limb against a tension spring in 67 anaesthetized dogs at 40,000 to 45,000 feet (12,190 to 12,315 metres) produced gas emphysema or gas embolism in 7 (11%), 3 of which had subcutaneous emphysema. Under the same conditions lowering of the blood pressure by intravenous injection of peptone or sorbital monolaurate was followed by the uniform collection of gas in the popliteal space, intermuscular fascia, and veins of the lower thigh and legs. *D. H. Sproull.*

The Significance of the Loss of Blood Volume into the Limbs during Pressure Breathing. HENRY, J. P. (1951). *J. Aviat. Med.*, **22**, 31.

The critical altitude above which the arterial oxygen saturation of man breathing oxygen at ambient pressure begins to fall is 40,000 feet (12,180 metres). To ensure survival above 45,000 feet (12,315 metres) it is necessary to increase the pressure of the gas around the man (as by a pressure suit), or of that in his lungs (by pressure breathing). The course of events in man breathing against a pressure 60 mm. Hg above ambient is described : they culminate in syncope, the result of blood pooling in the systemic veins. Not more than 25% of the total blood volume can be spared in this manner. It was found that syncope occurred earlier the higher the ambient temperature : plethysmographic studies showed that the rate of increase in leg volume during pressure breathing is correspondingly dependent on the ambient temperature. Even if the subject can compensate for the rapid pooling of blood in the limbs, syncope will eventually occur : this is attributed to the haemoconcentration which follows the abnormal distribution of the blood, and is due to loss of plasma water to the extracellular fluid in the area of the pooling. The haemoconcentration is greater at higher ambient temperatures. Over 30-minute periods of pressure breathing at room temperature an approximately linear relationship was found between the percentage decrease in p'asma volume (calculated from the packed cell volumes) and the breathing pressure. The loss of effective circulating blood volume, due to the rapid pooling of blood in the systemic veins and the more insidious haemoconcentration, is considered to be the cause of the eventual collapse.

It is concluded that for very high altitude flying some form of emergency pressure suit is a necessity.

D. H. Sproull.

S.29

. . . ANOTHER UNUSUAL USE FOR **'Sleek'**

plastic zinc oxide adhesive strapping

Fisher girls gutting the herring at an East Coast port were quick to discover the unique moisture-proof protective qualities of 'Sleek'. "I'll never be without it now," says one, showing her 'Sleek'-bound fingers.

Yes, 'Sleek' does get put to some intriguing uses. These unusual jobs lend dramatic emphasis to the unique qualities which make 'Sleek' of **outstanding value for everyday use in hospital and surgery practice.** Above all, because the plastic base material is impervious to liquids, it is waterproof. 'Sleek' is washable, yet does not soil easily. It is smooth and thin yet very strong. It is extensible and pliable. It does not 'catch' or fray.

to emphasise
8 valuable qualities

WATERPROOF · GREASEPROOF · WASHABLE · SMOOTH · THIN
STRONG · PLIABLE · NON-FRAYING

'Sleek' TRADE MARK **plastic zinc oxide adhesive strapping**

In 2½ yd. rolls, 1" wide. In 5 yd. rolls, 1", 2", 3" and 4" wide.

FREE SAMPLE sent on request

HERTS PHARMACEUTICALS LTD., WELWYN GARDEN CITY, ENGLAND

H V

Bandage—or barrier?

Industrial dermatitis *can* be avoided—safely, simply—if the worker uses Rozalex. It is effective against almost every known industrial irritant, and has been used in many factories for over 20 years. Quick and easy to use. Rozalex is accepted as the standard barrier preparation for industry. There is a type for every trade. May we send you free sample tins and a copy of "Skin Protection in Industry"?

ROZALEX DERMATITIS BARRIER PREPARATIONS

ROZALEX LIMITED, 10 NORFOLK STREET, MANCHESTER 2

RESPIRATORS *for work in Poisonous, Noxious, and Irritant Fumes*

DUST MASKS, ACIDPROOF AND WATERPROOF CLOTHING SAFETY GOGGLES, etc.

SELF-CONTAINED

OXYGEN BREATHING APPARATUS

for work in irrespirable atmospheres AND COMPRESSED AIR TYPES

RESUSCITATION APPARATUS

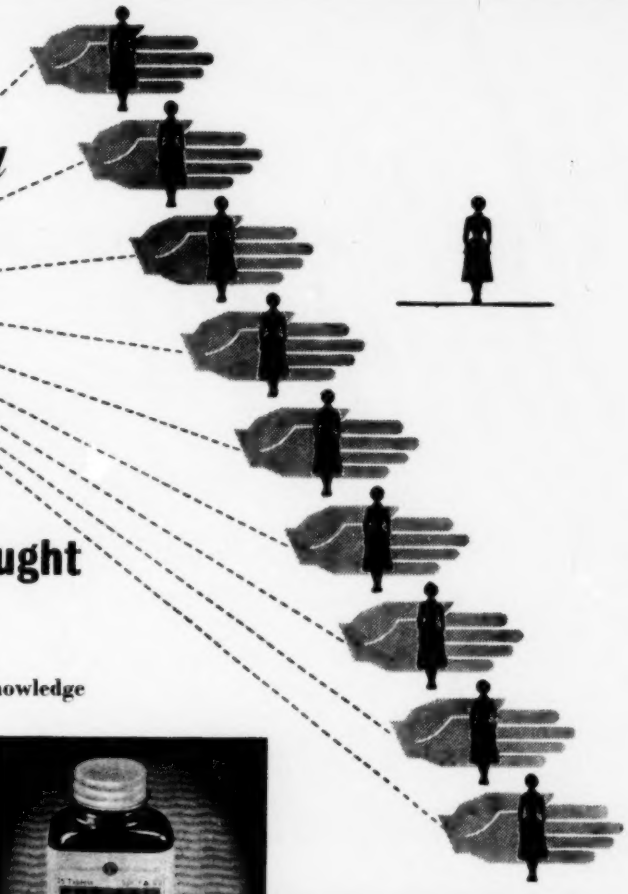
For reviving persons asphyxiated by poison gas or shock, Drinker Respirators (Iron Lung), OXYGEN TENTS, NASAL MASKS, GAS ANALYSIS APPARATUS, etc.

SIEBE, GORMAN & CO. LTD
LONDON
EVERYTHING FOR SAFETY EVERYWHERE

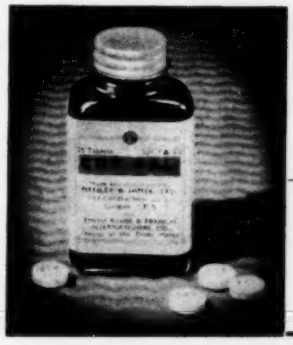
TOLWORTH, SURBITON, SURREY

In dysmenorrhoea

9 out of every 10 received the relief they sought



'We use it [Edrisal] with the knowledge that 9 out of 10 sufferers will get the relief they seek, and that without loss of time they can return to the production line in complete comfort.'



Each tablet contains: amphetamine ('Benzedrine') sulphate 2·5 mg., acetylsalicylic acid 160 mg., phenacetin 160 mg.

Two studies* amongst factory and office workers revealed that with 'Edrisal' nine out of every ten dysmenorrhoea sufferers received the relief they sought. The analgesic properties of 'Edrisal' are enhanced by the unique anti-depressant properties of its 'Benzedrine' component. 'Edrisal', therefore, not only relieves the pain during the menstrual period but also combats the accompanying psychic depression. In primary dysmenorrhoea the best results are usually obtained with a dosage of two 'Edrisal' tablets, repeated every three hours, if necessary. Samples are available on request.

* *Industr. Med.*, **15**, 262, 1946; **15**, 679, 1946.

'EDRISAL'

Its dual action relieves pain . . . elevates mood

MENLEY & JAMES, LTD., 123 COLDHARBOUR LANE, LONDON, S.E.5

for *Smith Kline & French International Co., owner of the trade marks 'Edrisal' and 'Benzedrine'*

ESP41

Intradex BRITISH DEXTRAN

A plasma substitute developed by British Scientists in Great Britain

The sixteen physical, chemical and biological tests, to which each batch of Intradex is subjected, ensure uniformity, sterility and freedom from toxic, pyrogenic, antigenic, anaphylactoid and cutaneous reactions.

It is interesting that each of a group of eight chinchilla rabbits, used to determine the renal excretion index, has received an average of approximately 1000 ml. of Intradex over a period of one year. This is equivalent to approximately 125 bottles (each 540 ml.) in a human subject. All these rabbits are in excellent condition.

Biological Control

The standard for freedom from pyrogenicity is more stringent than the B.P. standard. Rabbits are injected intravenously with 20 ml. Intradex per kg. of body weight. The batch of Intradex is rejected if any single rabbit in a group of six has a rise in temperature greater than 0.6°C. within four hours of the injection.

★

Available in M.R.C. transfusion bottles. Intradex (Salt Free) can be supplied for paediatric use and for the treatment of nephrotic cases. Further information and literature on request.

★

Intradex is the brand of dextran tested by the Medical Research Council and supplied to the Ministry of Health in Gt. Britain.

Manufactured by :

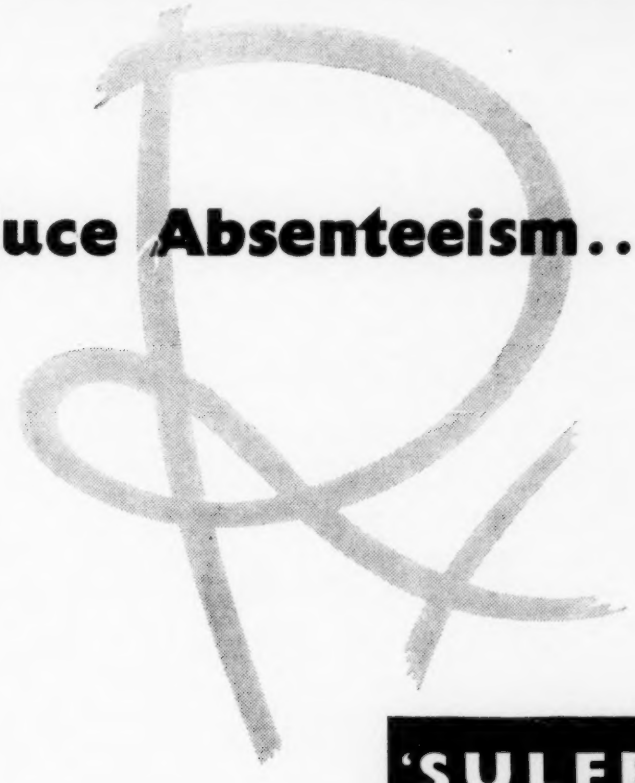
DEXTRAN LIMITED

AYCLIFFE · DARLINGTON

Sole Distributors :

THE CROOKES LABORATORIES LIMITED · PARK ROYAL · LONDON · N.W.10

Reduce Absenteeism...



'SULFEX'

The works medical officer who prescribes 'Sulfex' does much towards reducing industrial absenteeism caused by the common cold. He provides not only relief from nasal congestion, but also prophylaxis against secondary invading organisms believed to be responsible for the severe late manifestations of the common cold. 'Sulfex' administered intranasally, at the first sign of a cold, is a valuable ally for promoting recovery.

'SULFEX' — Vasoconstriction in minutes...

...bacteriostasis for hours

MENLEY & JAMES, LIMITED, COLDHARBOUR LANE, LONDON, S.E.5

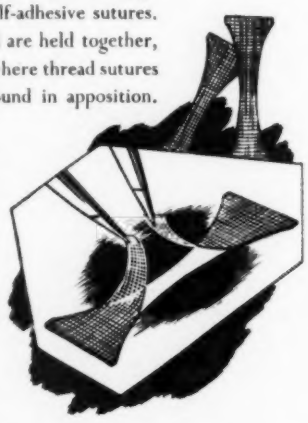
for *Smith Kline & French International Co., owner of the trade mark 'Sulfex'*

SXP101

SUTURING WITHOUT STITCHING

Inserting stitches in a wound causes the patient much pain and the doctor an expenditure of valuable time.

A new technique is available whereby, in many instances, the ordinary stitching of wounds can be superseded to the advantage of patient and practitioner alike. It is the use of Dalmas Dumb Bell self-adhesive sutures. Strips are laid across the incision or lesion, while the edges of the wound are held together, and gentle pressure by the finger assures a firm stay. They are also handy where thread sutures have broken apart and it is still essential to keep the edges of the wound in apposition.



Dalmas Dumb Bell stick-on sutures will be found invaluable for casualty and emergency work in surgeries, hospitals and factories. They provide safe and speedy co-aptation of wound edges, with freedom from the unpleasant effects of stitching and disfigurement through stitch holes.

Write on your printed notehead for specimens.

DALMAS

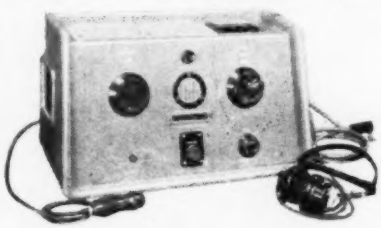
DUMB BELL SUTURES

safe . . . serviceable . . . speedy

Dalmas Ltd Junior Street Leicester telephone 65261 • London, Glasgow, Belfast and Overseas. Established 1823

Aurally Speaking

In the measurement of hearing loss, the Pure Tone Audiometer, TF895, conforms to the specification of the Committee on Electro-Acoustics appointed by the Medical Research Council. Each instrument is individually calibrated against N.P.L. determinations and will therefore provide a reading, on a given patient, comparable with that of any other Marconi Audiometer. Orally instructed through a crystal microphone and high-fidelity earphones, the patient responds via a signal lamp built-in to the instrument panel. Please ask for further information of this improved aid to audiometry.



PURE TONE AUDIOMETER
TYPE TF 895

MARCONI instruments

MARCONI INSTRUMENTS LTD., ST. ALBANS, HERTS. TELEPHONE: ST. ALBANS 6161/7

Marconi House, Pudding Chare, Newcastle on Tyne • 233 St. Vincent Street, Glasgow • Marconi House, 38 Pall Mall, Liverpool
Marconi House, Mount Stuart Square, Cardiff • 19 The Parade, Leamington Spa • 41 Donegall Place, Belfast

CONTUSOL

Brand (Regd.)

SOLUTION OF HEPARIN

New treatment for **BRUISES, LACERATIONS** and **CONTUSED WOUNDS**

available as

CONTUSOL LOTION for general application to bruises, sprains, etc., where the skin is not broken.

CONTUSOL ANTISEPTIC with Cetrimide and Aminacrine Hydrochloride as antiseptics for treatment of contused wounds.

INDUSTRIAL MEDICAL OFFICERS
are invited to write for one or more copies of our new comprehensive Catalogue, covering Medical, Surgical and Physiotherapy requirements.

REYNOLDS & BRANSON LTD.
LEODIS WORKS
NORTH WEST ROAD, LEEDS, YORKSHIRE
Telephone: LEEDS 29351 (5 lines). Telegrams: Reynolds, Leeds

MAKERS OF THE WELL-KNOWN INDUSTRIAL HAND CLEANSER "NESCO"

Saroul

provides safety against industrial skin diseases

Saroul Hand Cleanser has a long record of valuable service in the control and relief of industrial skin infections. It is antiseptic, emollient, beneficial to the skin — and THOROUGH! The most ingrained grease, pitch, oil, etc., yields immediately to an application.

Full information, sample, composition, etc., on request.

SANDEMAN BROTHERS LTD
BILSLAND DRIVE
MARYHILL GLASGOW

DIPLOMA IN INDUSTRIAL HEALTH
of the
SOCIETY OF APOTHECARIES OF LONDON

The Society of Apothecaries of London, conscious of the paramount importance of an efficient health service in Industry, has instituted this Diploma in Industrial Health, which is of a very high standard and is open to registered medical practitioners, members of H.M. Services, and others, such as Examining Surgeons, etc.

The Examination — which consists of four Papers, Oral and Clinical — is held in July and December.

The next Examination begins on July 7th, 1952.

Regulations and Forms of Application for Admission to the Examinations may be obtained from:

The Registrar,
SOCIETY OF APOTHECARIES OF LONDON
BLACK FRIARS LANE, E.C.4

SLIT SAMPLER for AIRBORNE BACTERIA

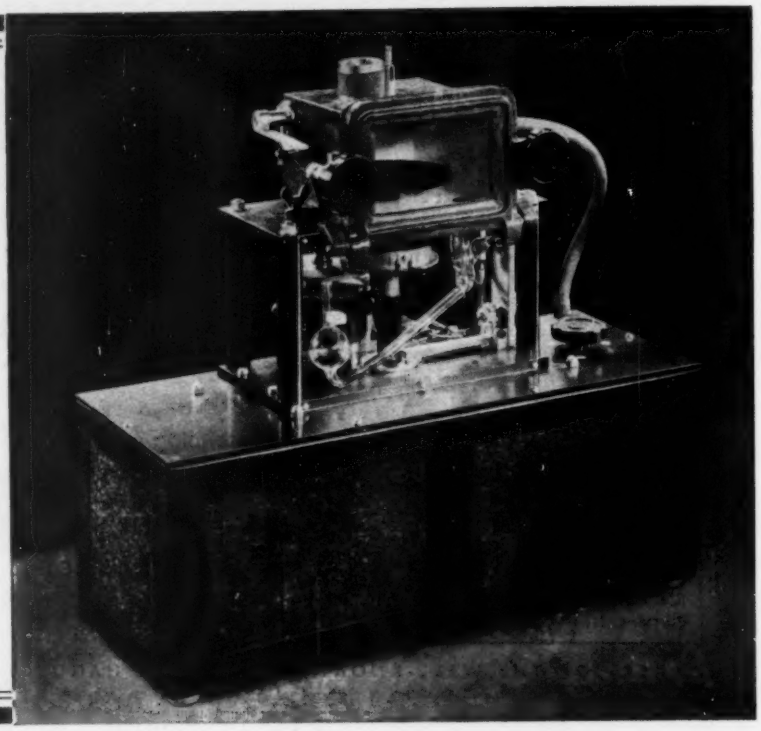
Three models available. For sampling air with up to 3000 organisms per 3 cubic feet and down to 1 organism per hundred cubic feet.

Available for early delivery—write for leaflet No. 759

C. F. CASELLA & Co. Ltd.

REGENT HOUSE
FITZROY SQUARE
LONDON, W.1

Telephone : ★EUSton 3944



MEDICAL RESEARCH COUNCIL

Industrial Health Research Board Reports

Because many I.H.R.B. Reports now out of print are still in demand, certain titles are to be reprinted. The first to appear will be :

No. 34. **A CONTRIBUTION TO THE STUDY OF THE HUMAN FACTOR IN THE CAUSATION OF ACCIDENTS**
by E. M. Newbold
Price 7s. 6d. By post 7s. 9d.

No. 61. **THE NERVOUS TEMPERAMENT**
by Millais Culpin and May Smith
Price 4s. 6d. By post 4s. 7½d.

No. 77. **FATIGUE AND BOREDOM IN REPETITIVE WORK**
by S. Wyatt and J. N. Langdon
assisted by F. G. L. Stock
Price 6s. 6d. By post 6s. 9d.

Other titles will follow in due course if the demand for these three is sufficiently large

Copies may be ordered in advance from:
H. M. STATIONERY OFFICE

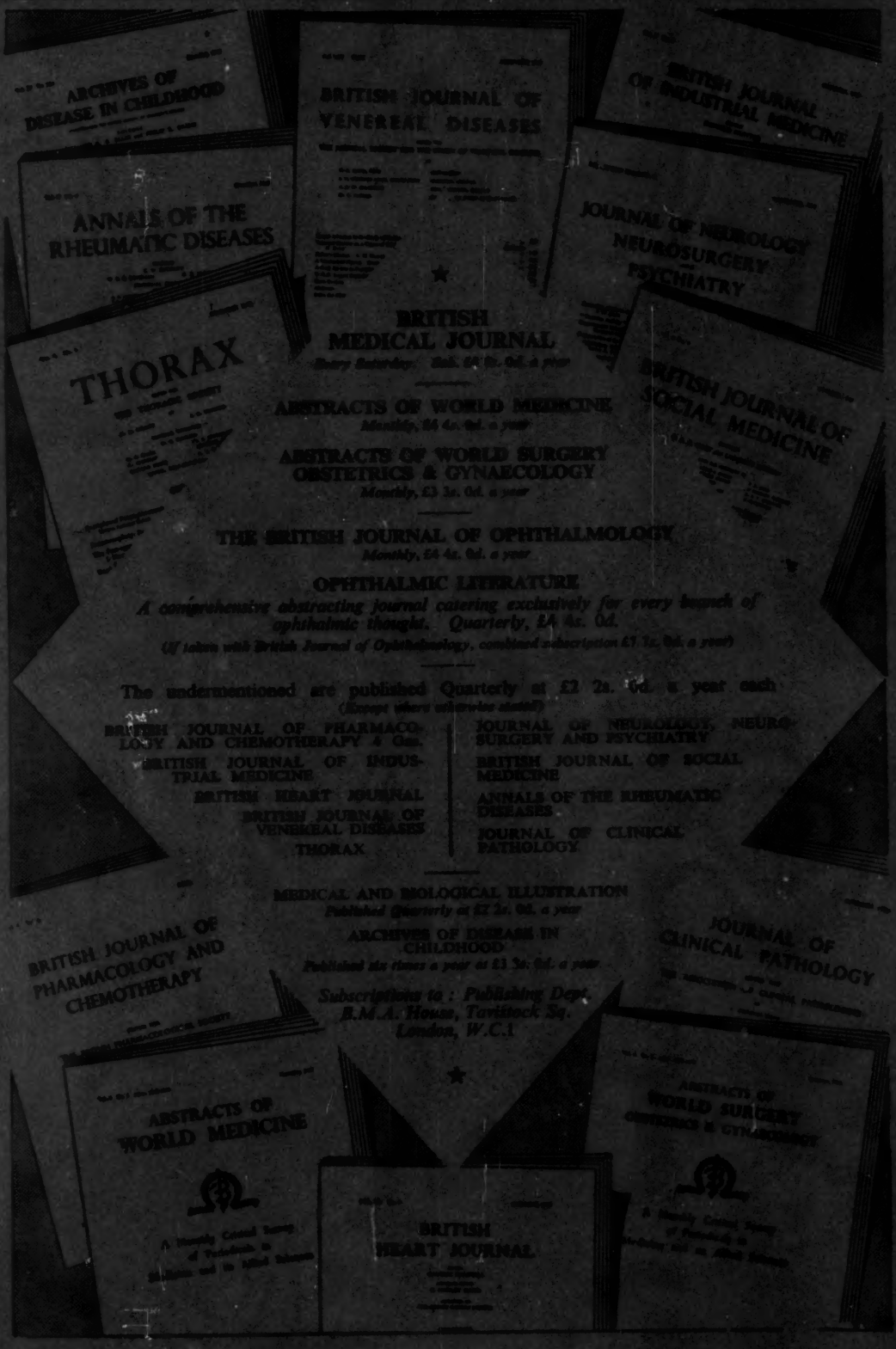
P.O. Box 569, London, S.E.1, and Sale Offices in London, Edinburgh, Manchester, Birmingham, Bristol, Cardiff and Belfast, or through any bookseller.

PNEUMOCONIOSIS

The Minister of National Insurance has referred to the Industrial Injuries Advisory Council for further consideration the question of the method of prescribing pneumoconiosis under the National Insurance (Industrial Injuries) Act, 1946, i.e., how the classes of insured persons eligible for benefit for the disease should be defined. The disease is at present prescribed by reference to a schedule of occupations which are known to give rise to a risk of the disease. These occupations are set out in Part II of the First Schedule to the National Insurance (Industrial Injuries) (Prescribed Diseases) Regulations, 1948 (S.I. 1948, No. 1371).

The Council propose to review this method of prescription and to consider possible alternatives, e.g., prescription generally for all insured persons, or by reference to occupations involving exposure to concentrations of specified dusts. The Council may also reconsider the definition of pneumoconiosis which for the purposes of the Act means "fibrosis of the lungs due to silica dust, asbestos dust or other dust, and includes the condition of the lungs known as dust-reticulation."

The Council are prepared to receive evidence from any persons or bodies interested who should communicate with their Secretary, **Mr. S. E. Waldron, O.B.E., Ministry of National Insurance, 30 Euston Square, London, N.W.1,** as soon as possible. An explanatory memorandum on the subject will be supplied on request.


ARCHIVES OF DISEASE IN CHILDHOOD
BRITISH JOURNAL OF VENEREAL DISEASES
BRITISH JOURNAL OF INDUSTRIAL MEDICINE
ANNALS OF THE RHEUMATIC DISEASES
JOURNAL OF NEUROLOGY NEUROSURGERY PSYCHIATRY
THORAX
BRITISH MEDICAL JOURNAL
Every Saturday. Sub. £4 2s. 0d. a year
BRITISH JOURNAL OF SOCIAL MEDICINE
ABSTRACTS OF WORLD MEDICINE
Monthly, £4 4s. 0d. a year
ABSTRACTS OF WORLD SURGERY OBSTETRICS & GYNAECOLOGY
Monthly, £3 3s. 0d. a year
THE BRITISH JOURNAL OF OPHTHALMOLOGY
Monthly, £4 4s. 0d. a year
OPHTHALMIC LITERATURE
A comprehensive abstracting journal catering exclusively for every branch of ophthalmic thought. Quarterly, £4 4s. 0d.
(If taken with British Journal of Ophthalmology, combined subscription £7 7s. 0d. a year)
The undermentioned are published Quarterly at £2 2s. 0d. a year each
(Except where otherwise stated)
BRITISH JOURNAL OF PHARMACOLOGY AND CHEMOTHERAPY 4 Gns.
BRITISH JOURNAL OF INDUSTRIAL MEDICINE
BRITISH HEART JOURNAL
BRITISH JOURNAL OF VENEREAL DISEASES
THORAX
JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
BRITISH JOURNAL OF SOCIAL MEDICINE
ANNALS OF THE RHEUMATIC DISEASES
JOURNAL OF CLINICAL PATHOLOGY
MEDICAL AND BIOLOGICAL ILLUSTRATION
Published Quarterly at £2 2s. 0d. a year
ARCHIVES OF DISEASE IN CHILDHOOD
Published six times a year at £3 3s. 0d. a year
Subscriptions to: Publishing Dept. B.M.A. House, Tavistock Sq. London, W.C.1
BRITISH JOURNAL OF PHARMACOLOGY AND CHEMOTHERAPY
JOURNAL OF CLINICAL PATHOLOGY
ABSTRACTS OF WORLD MEDICINE
A Monthly Critical Survey of Progress in Medicine and its Allied Sciences
BRITISH HEART JOURNAL
ABSTRACTS OF WORLD SURGERY
A Monthly Critical Survey of Progress in Medicine and its Allied Sciences

SLIT SAMPLER for AIRBORNE BACTERIA

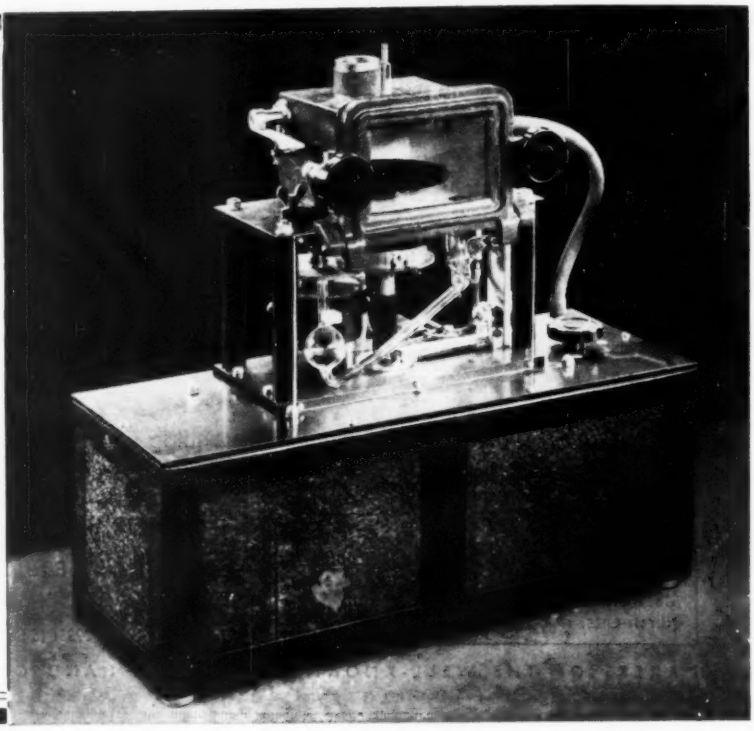
Three models available. For sampling air with up to 3000 organisms per 3 cubic feet and down to 1 organism per hundred cubic feet.

Available for early delivery—write for leaflet No. 759

C. F. CASELLA & Co. Ltd.

REGENT HOUSE
FITZROY SQUARE
LONDON, W.1

Telephone : ★EUSton 3944



MEDICAL RESEARCH COUNCIL

Industrial Health Research Board Reports

Because many I.H.R.B. Reports now out of print are still in demand, certain titles are to be reprinted. The first to appear will be :

No. 34. **A CONTRIBUTION TO THE STUDY OF THE HUMAN FACTOR IN THE CAUSATION OF ACCIDENTS**
by E. M. Newbold
Price 7s. 6d. By post 7s. 9d.

No. 61. **THE NERVOUS TEMPERAMENT**
by Millais Culpin and May Smith
Price 4s. 6d. By post 4s. 7½d.

No. 77. **FATIGUE AND BOREDOM IN REPETITIVE WORK**
by S. Wyatt and J. N. Langdon
assisted by F. G. L. Stock
Price 6s. 6d. By post 6s. 9d.

Other titles will follow in due course if the demand for these three is sufficiently large

Copies may be ordered in advance from :

H. M. STATIONERY OFFICE

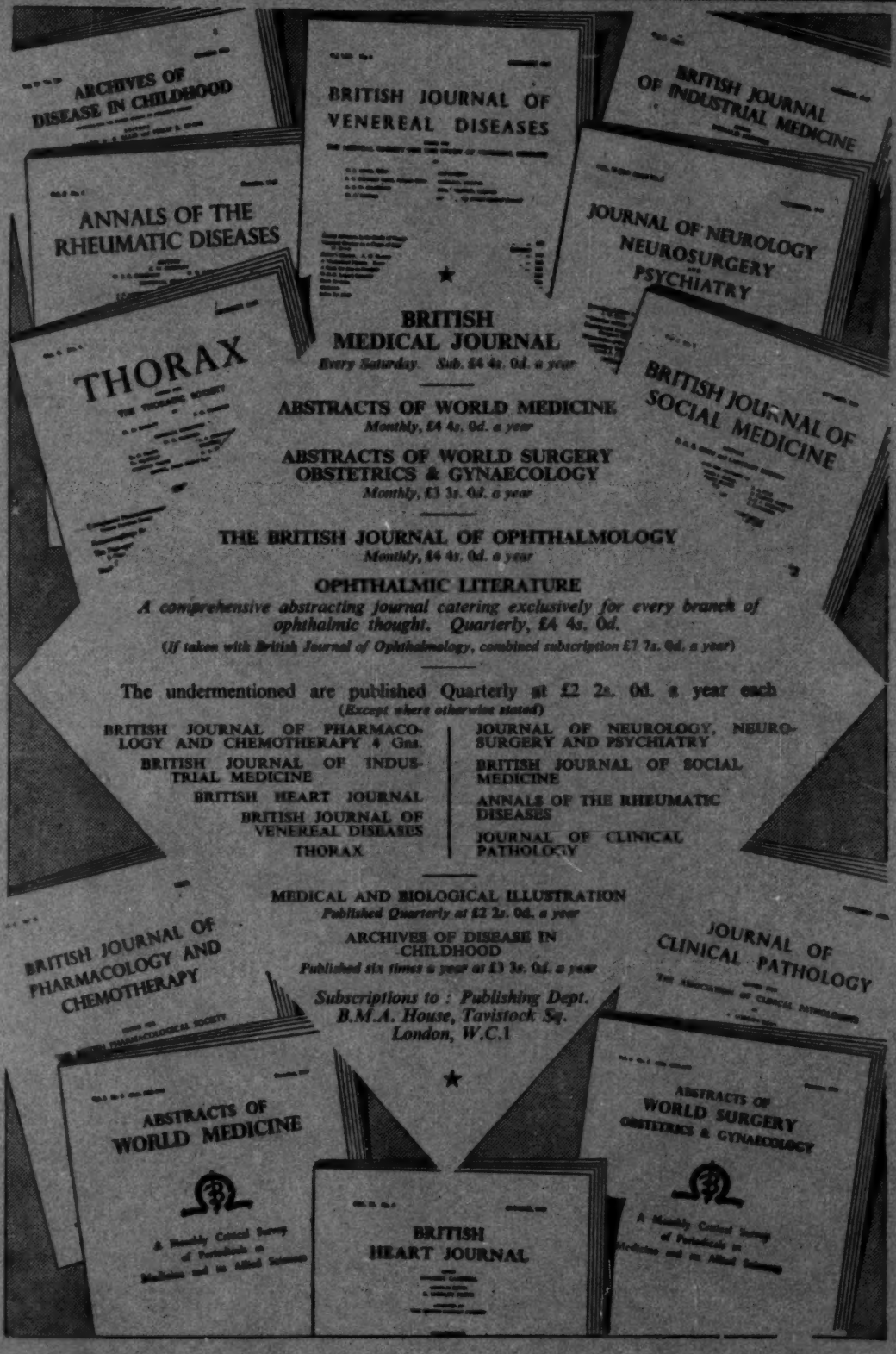
P.O. Box 569, London, S.E.1, and Sale Offices in London, Edinburgh, Manchester, Birmingham, Bristol, Cardiff and Belfast, or through any bookseller.

PNEUMOCONIOSIS

The Minister of National Insurance has referred to the Industrial Injuries Advisory Council for further consideration the question of the method of prescribing pneumoconiosis under the National Insurance (Industrial Injuries) Act, 1946, i.e., how the classes of insured persons eligible for benefit for the disease should be defined. The disease is at present prescribed by reference to a schedule of occupations which are known to give rise to a risk of the disease. These occupations are set out in Part II of the First Schedule to the National Insurance (Industrial Injuries) (Prescribed Diseases) Regulations, 1948 (S.I. 1948, No. 1371).

The Council propose to review this method of prescription and to consider possible alternatives, e.g., prescription generally for all insured persons, or by reference to occupations involving exposure to concentrations of specified dusts. The Council may also reconsider the definition of pneumoconiosis which for the purposes of the Act means "fibrosis of the lungs due to silica dust, asbestos dust or other dust, and includes the condition of the lungs known as dust-reticulation."

The Council are prepared to receive evidence from any persons or bodies interested who should communicate with their Secretary, **Mr. S. E. Waldron, O.B.E., Ministry of National Insurance, 30 Euston Square, London, N.W.1,** as soon as possible. An explanatory memorandum on the subject will be supplied on request.


ARCHIVES OF DISEASE IN CHILDHOOD
BRITISH JOURNAL OF VENEREAL DISEASES
BRITISH JOURNAL OF INDUSTRIAL MEDICINE
ANNALS OF THE RHEUMATIC DISEASES
JOURNAL OF NEUROLOGY NEUROSURGERY PSYCHIATRY
THORAX
BRITISH JOURNAL OF SOCIAL MEDICINE
BRITISH JOURNAL OF PHARMACOLOGY AND CHEMOTHERAPY
JOURNAL OF CLINICAL PATHOLOGY
ABSTRACTS OF WORLD MEDICINE
ABSTRACTS OF WORLD SURGERY OBSTETRICS & GYNAECOLOGY
BRITISH HEART JOURNAL

BRITISH MEDICAL JOURNAL
Every Saturday. Sub. £4 4s. 0d. a year

ABSTRACTS OF WORLD MEDICINE
Monthly, £4 4s. 0d. a year

ABSTRACTS OF WORLD SURGERY OBSTETRICS & GYNAECOLOGY
Monthly, £3 3s. 0d. a year

THE BRITISH JOURNAL OF OPHTHALMOLOGY
Monthly, £4 4s. 0d. a year

OPHTHALMIC LITERATURE
A comprehensive abstracting journal catering exclusively for every branch of ophthalmic thought. Quarterly, £4 4s. 0d.
(If taken with British Journal of Ophthalmology, combined subscription £7 7s. 0d. a year)

The undermentioned are published Quarterly at £2 2s. 0d. a year each
(Except where otherwise stated)

BRITISH JOURNAL OF PHARMACOLOGY AND CHEMOTHERAPY 4 Gns.
BRITISH JOURNAL OF INDUSTRIAL MEDICINE
BRITISH HEART JOURNAL
BRITISH JOURNAL OF VENEREAL DISEASES
THORAX
JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
BRITISH JOURNAL OF SOCIAL MEDICINE
ANNALS OF THE RHEUMATIC DISEASES
JOURNAL OF CLINICAL PATHOLOGY

MEDICAL AND BIOLOGICAL ILLUSTRATION
Published Quarterly at £2 2s. 0d. a year

ARCHIVES OF DISEASE IN CHILDHOOD
Published six times a year at £3 3s. 0d. a year

Subscriptions to : Publishing Dept. B.M.A. House, Tavistock Sq. London, W.C.1

ZŌPLA

STRAPPING

Zōpla Strapping is a first-class product for surgical use. Very strong cloths, the make is powerfully adhesive. White and Flesh Cloths, also on Elastic Cloth.

WHITE FELT

Zōpla on White Felt is very popular for padding and protective purposes. Does not harden in use.

HELVIA

First-Aid Flexible Dressing Elastic adhesive plaster with medicated gauze.

MANUFACTURED BY
LESLIES LTD
EST. 1823

HIGHAM HILL RD.
WALTHAMSTOW
LONDON, E.17.

Sternocleanse

protects the working hand

Sternol Sternocleanse

COMPOSITION: Sodium Stearate (Commercial); Glycerine (Pure); Kaolin; plus a small percentage of Para Chlor Meta Cresol.

For a cost of ½d. per man per day, Sternocleanse will safeguard production and overheads. Sternocleanse is used in many of Britain's largest factories because, after severe clinical and practical tests, it proved itself to be the most satisfactory antidermatitis cream—both antiseptically and economically.

Why not make a practical test yourself? Write today for a sample tin.

STERNOL LIMITED, Royal London House, Finsbury Square, London, E.C.2
Telephone: MONarch 3871-5
Telegrams: Sternoline, Phone, London

Printed in England by Hazell, Watson & Viney, Ltd., London and Aylesbury—1878–51